Equity in the Access to Medicines:
The Importance of Incentivizing and Protecting Follow-on Innovation

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Equitable access to medicines expands when a variety of treatment options are available, including specialized versions for vulnerable populations and affordable generics. Investments in the research and development of these treatments are incentivized by a legal ecosystem that protects innovation. Continued innovation delivers medicines that are safer, encourages treatment adherence, and facilitates access for a diversity of patients. Fundamentally, follow-on innovation enhances equitable access.

Key Takeaways:

- Medicines and biopharmaceutical products enhance and extend lives, providing benefits that should be widely available. The iterative nature of biopharmaceutical innovation ensures that first-in-class innovations are improved upon through continuing innovation, a process that results in a variety of therapeutic options for patients.
- Follow-on innovations increase the number of therapeutic options, enabling many disadvantaged and vulnerable populations to access healthcare advances that may not otherwise be available.
- The investments that generate follow-on innovations must be incentivized. Empirical evidence establishes that innovation happens when legal and regulatory mechanisms protect innovation. A vibrant patent system and effective enforcement are essential.
- Follow-on innovations address disparities in health care. While affordable generic drugs address financial constraints, it is also important to facilitate access for patients with physiological constraints – such as children and geriatric patients – and those residing in resource-limited locations – such as those without access to refrigeration or trained medical personnel.
- Follow-on innovation must be encouraged and supported. Policymaking should be driven by rigorous empirical evidence and transparent research methodologies. Demands to amend existing laws and regulations are misdirected unless based in facts and empirics.

"The cumulative effect of numerous minor incremental innovations can sometimes be more transforming and have more economic impact than a few radical innovations of 'technological breakthroughs.'"
The National Research Council, 1996[1]

I. INTRODUCTION

Discussions surrounding pharmaceutical patent policy are contentious and vitriolic, with those on both sides passionately advocating their positions. At the heart of the debate is access to medicines: access for *more* people to *more* treatments and cures. All indicators suggest that the majority of medical progress is happening through incremental innovation.[2] The value and importance of follow-on innovation has been extensively documented, and numerous studies establish the health benefits, economic benefits, and welfare gains that these improvements and alternatives generate.[3] Follow-on innovation ensures that the benefits of modern medicine are more widely available, including to disadvantaged and vulnerable populations. Importantly, the provision of these health benefits and equitable access would not be possible without patents and other forms of intellectual property (IP) protection.

Access to Medicines

The failure to facilitate greater access to medicines is perhaps the sharpest and most poignant criticism of the biopharmaceutical industry, and one that resonates with patients and policymakers alike. The root cause of this failure, critics allege, is a patent system that "enables drug companies to get hundreds of patents – effectively doubling the length of their monopoly. monopoly. This allows companies to set prices far too high for far too long."[4] Admittedly, lack of access to medicine *is* a problem and critics are justified in drawing attention to the issue. However, assigning blame to the patent system as the cause of the problem is fundamentally flawed.

As with many difficult things, the devil is in the details. The simple story put forward by critics barely scratches the surface of a more complicated and nuanced reality. Their story goes like this: access is a problem because affordable generics are not available and that is because of the patents and exclusivity-extending strategies employed by the biopharmaceutical industry. Primary among the criticisms is the allegation of evergreening[5], though the term is frustratingly unclear and has recently been expanded to encompass a wide range of strategies, some patent-related and some not.[6] A recent study by Erika Lietzan (2020) describes how "allegations of 'evergreening' pervade legal scholarship, economic scholarship, medical and health policy scholarship, and policy writing" through an exhaustive analysis of the variety of definitions, their claims and empirical studies. In contrast, according to the recent report by the International generic and Biosimilar Medicines Association, "Evergreening" strategies include: (1) patent thickets; (2) patent linkage; (3) elimination of skinny labels; (4) product hopping; (5) pricing strategies; (6) denigration of off-patent products, and (7) misuse of regulatory exclusivities. The expanse of this list makes it clear that "evergreening" is a sloppy metaphor covering a collection of practices that are overwhelmingly legal and valid.

Intellectual Property Rights as Incentives

The challenges surrounding access are significant, and unfortunately difficult to tackle. This is particularly true of equitable access for small and disadvantaged populations. The research and development of biopharmaceutical products is expensive, risky and time consuming. According to the most recent report by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), only 1-2 of every 10,000 compounds synthesized eventually becomes a medicine, the time to development of a new medicine can take 10-15 years, and the cost of that development averages USD $2.6 billion, when accounting for failed development efforts.[7] Drugs are costly to develop and easy to copy. Because of this, intellectual property rights are needed to incentivize their development. The

resources invested in this process must be recovered and the patent system facilitates this by balancing the incentives to innovate with a short period of exclusivity. This is true of both breakthrough therapies as well as follow-on innovations.

Given that the challenges of access persist, they attract a great deal of attention from industry critics[8], government policymakers[9], academics[10], and patient groups. Demands for change and proposals date back decades, with recommendations spanning small tweaks to the complete dismantling of the existing system.[11] As described by the World Trade Organization (WTO), the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was an early endeavor to address the challenges surrounding access to medicine, particularly in developing nations. While TRIPS aims to protect intellectual property, including pharmaceutical patents, it also includes flexibilities that allow countries to address potential barriers to access to medicines, particularly in developing nations. Until recently, objective empirical analysis of the patent policy debate has been hard to come by.

USPTO Report on Drug Patents

The long-awaited USPTO report, "Drug Patent and Exclusivity Study", is a shining example of getting things right, and the importance of evidence-based work informing policymaking.[12] The report examines how intellectual property fuels innovation across industries, noting that innovation is an iterative process, building upon the knowledge and advancements of those that came before. Through the disclosure of knowledge and the provision of incentives for research and development, the patent system accelerates innovation. This system incentivizes both first-in-class drugs and the follow-on innovations that embody improvements in safety and efficacy. Without patents and other forms of IP protection, these treatments and cures would not be developed. While these advances improve and extend our lives, they also ensure that there is greater *equity* in access to medicines, which is the focus of this policy brief.

Equity in Access

The benefits of modern medicine should be available to all, irrespective of their circumstances or constraints, be they financial, physical, or geographic. Follow-on innovation addresses disparities in healthcare. While affordable generic drugs address financial constraints, it is also important to facilitate access for patients with physiological constraints and those residing in resource-limited locations. Specifically, equitable access means access for all, including disadvantaged and vulnerable populations such as children, geriatric patients, and those in the developing world.

The truth is nuanced and complicated, such that there is no simple mechanism for enhancing access to medicines. The subtleties of each strategy, and perhaps each case, must be taken into account in order to precisely identify the issue, determine if a remedy is needed and if so, what the best remedy would be. This is difficult and cannot be accomplished with a one-size-fits-all or one-patent-per-molecule policy. The extent of the changes being demanded by some commentators and policymakers and the radical nature of the policy recommendations should alert us to their magnitude and the necessity of caution and rigor in evaluating any policy changes. This is particularly true in light of the fact that the existing system is mostly *working* well to deliver a constant flow of new treatments to patients.

II. IMPORTANCE OF ACCESS

As noted, the existing debate over biopharmaceutical policy is contentious and vitriolic, with a focus on the technical details of national patent laws and their influence on market forces. At the root of these discussions is a struggle over access to medicines: what medicines are available, how quickly, for whom, and at what price. Positions are passionately defended because of the tremendous potential for modern

medicine to improve and extend our lives. And here is what both sides agree on: These are benefits to which we want everyone to have access.

In the context of the biopharmaceutical industry, radical innovations encompass breakthrough discoveries of a "first-in-class" medicine with a new mechanism of action. In contrast, incremental or follow-on innovations may expand an existing therapeutic class through the development of a new drug based on differences in adverse effects, delivery systems, dosing schedules, or heat stability. These are therapies that largely replicate the action of existing drugs and this is where medical progress is happening. Importantly, this innovation is happening in the labs of both innovation biopharmaceutical firms and generic and biosimilar firms.

From a public health perspective, incremental innovation ensures that several drugs are available within a therapeutic class which provides physicians with flexibility in treating the specific needs of diverse patients with precision. For patients, the benefits can be tremendous. Therapeutic alternatives within the same drug class may differ in their metabolism, molecule, regimen, dosing schedules, speed of action, delivery system, adverse effects, therapeutic profile, and/or interactions.[13] These differences increase a patient's probability of finding a treatment that is both effective and tolerated. In addition, innovative improvements have the potential to increase the number of available dosing options, uncover new physiological interactions of known medicines, allow for reformulations to encourage children's compliance, increase the shelf-life or heat-stability of a given medicine to secure effectiveness in diverse environments, eliminate treatment-limiting drug reactions or side effects, enhance patient administration and improve patient compliance. Moreover, multiple therapies ensure an uninterrupted supply and availability of vital medications if the initial drug fails in the development stage, in the market, or suffers from manufacturing interruptions.[14]

Biopharmaceuticals provide benefits to patients and to national healthcare systems. They enhance the quality and length of our lives and generate savings across the health system. While patients have access to more novel therapies than ever before, the share of prescriptions filled as generic drugs increased from 18.6 percent in 1984 to 91 percent in 2022, with more than 32,000 generic drugs approved by the FDA to date, evidence that the competitive market now provides more of both, innovator and generic drugs.[15,16]

These benefits should be widely available, irrespective of financial, physical, or geographic constraints. Generic drugs are more affordable, addressing financial constraints, but access must be facilitated for patients with physiological constraints and those residing in resource-limited locations as well. Specifically, equitable access means access for all, including children, geriatric patients, and those in the developing world.

III. SOLUTION TO THE CHALLENGE OF EQUITY IN ACCESS

To ensure equity in access, more innovation is needed, not less. In many cases, additional innovation is needed to modify drugs for disadvantaged populations and resource-limited settings. Notably, follow-on innovations "address disparities in health care".[17] Given that biopharmaceutical innovation is subject to numerous market failures, incentives are needed to induce industry research and development.[18] Patents and other forms of intellectual property rights ensure that innovation is protected and the investments that made them possible are rewarded, thus incentivizing biopharmaceutical research. Patent rights were enshrined in the U.S. Constitution more than 230 years ago, providing a key driver of the economic prosperity that continues today. The patent system facilitates the innovation that has enabled the U.S. biopharmaceutical industry to thrive. Currently, more than half of global R&D efforts are conducted by U.S. firms.[19, 20]

Patentability of New Drugs

To be patentable in the United States, an invention must be novel, non-obvious, and useful. Specifically, U.S. patent law considers "any new and useful process, machine, manufacture, or composition of matter, or any new and useful *improvement* thereof"[21] as patent eligible subject matter. Meeting that standard, a patent is awarded and lasts for 20 years – regardless of the subject matter or the jurisdiction. However, new medicines occupy a complex landscape subject to patent law and several others: "the federal framework requiring premarket approval of new medicines and their copies, federal intellectual property laws, federal and state laws governing promotion of medicines, and federal laws and practices and state laws relating to prescribing and dispensing of medicines" (doctors and pharmacists).[22] As a result, the introduction of a new medicine is subject to a web of legal and regulatory conditions that must all be satisfied before market launch.

In brief, new medicines must undergo premarket testing and seek approval from the U.S. Food and Drug Administration (FDA). Upon launch, they are usually sold under brand names and protected by patents and statutory rights in the testing data. The protection provided by these intellectual property rights delays the approval and introduction of generic versions. Eventually less expensive generic versions are approved by the FDA, which pharmacists then usually dispense automatically, even when doctors prescribe the branded product by name.[23]

Time and Cost Needed for Drug Development

Innovator drugs are admittedly more expensive than generic versions, and that is because they are more expensive, difficult, and risky to produce and develop. Specifically, for innovative pharmaceutical products, the fixed costs of drug development are generally large relative to the marginal costs of production. In contrast, generic manufactures bear the much more modest costs of imitation.[24] This stark difference characterizes both the time required for development, as well as the financial resources needed, as shown in the table below. Current estimates indicate that innovation-based companies spend between 157 and 446 times that which generic companies spend on the development of a particular drug. Post-development innovative medicines still face significant market uncertainty. Vernon, Golec and DiMasi (2010) find that only two in ten marketed drugs return revenues that match or exceed research and development costs.[25] These differences point to the necessity of strong IP protection to ensure a well-functioning biopharmaceutical ecosystem. That is, patents are necessary as incentive tools because of the high failure rate in drug development. The biopharmaceutical business model relies on revenues from the minority of "wins" to cover the majority of "losses". Continued investment and innovation depend upon strong intellectual property protection and the innovative firms' ability to recoup their investments.

Drug Development Process and Comparisons[26]

Drug Development Phases	Innovative Companies	Generic Companies
Research and Development	2-6.5 years [a, f] (early-stage development)	6 months – 1 year [a] (secure active ingredient and formulation)
Tests and Trials	7 years [a, e]	3-6 months [a]
Time from Laboratory to Market	11-13 years [a] 12-14 years [g]	2.25-6.5 years [a] 3-5 years [c, d]
Estimated Total Costs	$314 million - $4.46 billion [h]	$2-10 million [b]
Time to Recoup Investments	6-9 years (EPL) [i]	No time limit

Comparing the time, risk, and costs of drug development across innovative and generic companies explains why the cost of an innovative drug will be greater than the cost of a generic drug that must only

cover the marginal cost of production. The investments undertaken by innovative firms, and protected by patents, benefit all patients, as is evidenced in the fact that 90% of U.S. prescriptions are filled with generic drugs which comprises only 13.1% of drug spending.[27]

Legal Landscape of the Biopharmaceutical Industry

Perhaps less evident is the fact that intellectual property rights also facilitate the development of generic medicines. Fundamentally, IP is essential for, and valuable to, both the innovative and generic industries.[28] According to a 2011 WIPO analysis of the patents on Ritonavir, a significant portion of the subsequent filers included generic companies. Specifically, Ranbaxy is listed in the WIPO analysis as one of the most common assignees.[29] While the patent system was designed to incentivize and reward innovation, and the Hatch-Waxman Act[30] and Biologics Price Competition and Innovation Act (BPCIA)[31] balance innovation and access to small molecule drugs and biologics. These two pieces of legislation established abbreviated pathways for biosimilars (through the BPCIA) and generic small-molecule drugs (through the Hatch-Waxman Act) to be approved by the U.S. FDA without repeating costly clinical trials to establish safety and efficacy.

The complexity of this legal landscape may be responsible for a number of misunderstandings regarding how the biopharmaceutical industry operates. Most often, critics erroneously claim that pharmaceutical companies "extend" patents in order to prolong market exclusivity and prevent generic competition.[32] Importantly, it is legally impossible to extend a patent.[33] Moreover, these situations never involve an extension of the company's proprietary rights in its research data, which is also legally impossible.[34] An innovator cannot receive two patents for the same invention. Accordingly, upon expiry, the claimed invention becomes part of the public domain, regardless of whether any continuation applications were filed.[35] Further, numerous studies of patenting in the biopharmaceutical industry document that companies usually face generic competition long before 20 years of a full patent term.[36]

In addition, the number of patents covering a particular drug is not a factor in generic competition entering the market, which is another inaccurate claim frequently made.[37] Further, the misguided claims of "patent thickets" are put to rest by the recent USPTO study which concludes that simply counting the number of patents on a product is not a reliable way to determine a drug's exclusivity period and "can be misleading." [38] Regardless of the type or extent of follow-on innovations an innovator patents and launches, once the patent on the original active ingredient expires, a generic company can use the ingredient in its own product *and* obtain approval relying on the research the innovator performed.[39,40] Specifically, the FDA's approval of a new dosage form does not preclude a generic company from copying the innovator's old dosage form, and there are no prohibitions to prevent this generic company from promoting its competing product to doctors, payers, and patients.[41] Finally, nothing prevent payers from requiring that their insured patients use the generic company's product.[42] Not only does follow-on innovation not preclude generic entry, it benefits patients by making therapeutic alternatives available, alternatives that are especially valuable to disadvantaged and resource-limited patient populations.[43]

Follow-on Innovation and Neglected Diseases

Another flawed argument makes the claim that incremental innovation takes resources away from more innovative work or research that is needed on neglected diseases. Development organizations working on behalf of third-world patients contend that 'me-too' and 'follow-on' drugs provide little or no therapeutic value over innovative drugs and that nations with limited resources suffer as a result.[44] This line of thinking is frequently accompanied by an argument advocating weakened patent protection, especially for developing nations, and/or the denial of patent protection for incremental innovation. [45] The economics of innovation suggest just the opposite. Through a stronger IP paradigm, innovative firms are encouraged to take on risk and invest scarce resources.

Contrary to the claim that patents for follow-on innovations discourage companies from undertaking the riskier and more expensive research that is required to generate breakthrough drugs, intellectual property rights foster valuable pharmaceutical innovation and speed the development of breakthrough therapies.[46] This conclusion is echoed in the work of Kyle and McGahan (2012) who studied innovations in nations that enhanced intellectual property protections in accordance with the WTO's TRIPS Agreement and those that did not. The study found that protecting innovation enhances research on cures, rather than inhibiting it. Their work finds evidence of more research on diseases in nations with TRIPS-compliant IP provisions as patent provisions were implemented than on diseases in non-TRIPS-compliant nations.[47] Implementing protections for innovation, including incremental innovation, generates the research that results in life-enhancing and extending treatments.

Development of Combination Therapies and New Treatments

Patent protection for follow-on innovations also facilitates the development of combination therapies and repurposed drugs. The potential for patent protection incentivizes research into combining existing active ingredients, which can lead to synergistic effects and improved treatment outcomes for complex diseases. For some medicines, later-issuing patents may be the only form of intellectual property incentivizing its development and protecting the product.[48] Ultimately, intellectual property rights should balance benefits of new drugs and the costs of the market exclusivity that patents guarantee.[49]

The existing patent system provides the incentives to conduct the R&D needed for new treatments and cures and, at the same time, facilitates the entry of generic and biosimilar versions. It is the essential remedy to the market failure – expensive to develop and cheap to copy – that would otherwise prevent the development of new medicines. Wider access to medicine is made possible through more innovation, more treatments, and cures, not fewer. Follow-on innovations are evidence of the success of the current IP ecosystem, expanding access through versions for pediatric populations, geriatric patients, individuals in resource-limited settings, and simplified modes of administration that facilitate treatment adherence.

IV. ACCESS IS ENHANCED WHEN INCENTIVES ARE WORKING

Equitable access is enhanced with the availability of a variety of therapeutic options. Patents and other forms of intellectual property rights incentivize the development of those therapies. The existing patent system provides those incentives, and we see it working. Nearly 40% of the drugs that have reached the market in the last decade have come from incremental innovation, evidence that the innovative pharmaceutical industry is developing both new drugs resulting from radical innovation as well as follow-on versions, improvements to existing products. Further, the majority of FDA and EMA (European Medicines Agency) Oncology Drug Approvals in the first quarter of 2025 were new indications for biologics and biosimilars. Together, the FDA and the EMA approved 39 new or expanded indications for previously approved agents and 4 new oncology agents in the first quarter of 2025.[50]

Equitable Access for Vulnerable Populations

Follow-on versions are especially crucial for equitable access for children, geriatric patients, resource-limited populations, cognitively impaired patients, and those who struggle with drug interactions or negative side effects. Follow-on innovations may take the form of new formulations which improve safety and efficacy, extend the dosing duration, or reduce side effects. Alternatively, the advances may come through new dosage forms or new administration routes which can improve patient treatment adherence. For children, continued research enables the development of dosages appropriate for smaller bodies and more fragile systems. Orally administrable formulations of drugs that could previously only be administered by more invasive intravenous or intramuscular injection can reduce the burden of healthcare providers and provide treatment options for patients without access to trained medical

personnel, those in rural areas or developing nations.[51] In the case of geriatric individuals, patient compliance can be improved by simplifying medication regimes through the development of a single-pill combination therapy that combines two or more active pharmaceutical agents in a single formulation. Finally, heat-stable formulations can make previously unavailable drugs accessible in resource-limited setting lacking refrigeration.

These advances are only possible because the IP system is functioning well, and the research is incentivized. Pharmaceutical development is a lengthy, risky process, and frequently a safe and effective drug emerges only after follow-on innovation that began long after the initial synthesis of a pharmaceutically interesting chemical compound. The resulting innovation, protected by later-issuing patents, may be as important for drug development as a patent on the active ingredient itself.[52]

Small steps and large leaps can both be life-changing. Examples abound.[53]

- Lipitor was not the first statin developed to treat high cholesterol, but it became the most widely prescribed drug in its class due to its superior safety and efficacy profile. The variety of available statins provide important therapeutic options for patients since there is "significant heterogeneity in the way in which patients respond, with as few as one in 50 patients benefiting from one single statin drug."[54]

- Prozac was launched in the United States in 1987 as a first-in-class therapy for the treatment of major depressive disorder. Prozac was an improvement over existing antidepressants that were associated with significant side effects. In 2001, a once-weekly formulation, protected by a separate patent, was launched to increase patient options and compliance.[55]

- Abraxane is a form of Taxol, which uses albumin to deliver the chemotherapy. This innovation avoids hypersensitivity, provides a greater tumor response rate, and makes it possible to administer the drug without steroids, which can cause problems from severe insomnia to very high blood sugars. SUBACAP is used to treat fungal infections. SUBACAP reduces inter-patient and intra-patient variability and therefore claims a more predictable clinical response enabling a reduction in active drug quantity to deliver therapeutic blood levels.

- Captopril was the first medicine to inhibit an enzyme, the angiotensin converting enzyme or "ACE," that was found to be linked to congestive heart failure. It was later discovered that captopril was accompanied by unpleasant side effects such as itching and headaches. Subsequent research and development to address the limitations of captopril not only eliminated unwanted effects but also yielded a completely new understanding of the enzyme involved.[56]

- Kombiglyze XR is the combination of two treatments, metformin and saxagliptin, which allows for a single dosage form, a much simpler drug therapy regimen for patients suffering from type 2 diabetes.[57]

- Not surprisingly, thriving within the industry ecosystem means that generic and biosimilar firms are also innovating, and relying on the same patent protection and intellectual property mechanisms that incentivize all innovation. The Generics and Biosimilars Initiative describes some key examples in the products of Abraxane and SUBACAP. Abraxane is a generic form of Taxol that delivers chemotherapy via albumin and thus avoids hypersensitivity and claims a greater tumor response rate. Such forms of innovation by the generic pharmaceutical industry can be observed in drug product design, formulation, process development and manufacturing processes going back to the initial stages of the product development cycle.[58]

Improving Medication Adherence

Follow-on therapies provide health gains to a diversity of patients and also improve medication adherence. The benefits to greater adherence are considerable, for patients, the healthcare system, and the economy. Treatment adherence impacts both the quality and length of life, health outcomes, and overall healthcare costs.[59] The total cost estimates for medication nonadherence range from $100 billion to $300 billion every year, when both direct and indirect costs are included.[60] And yet, seventy-five percent of Americans have trouble taking their medicine as directed.[61] Nonadherence can account for up to 50% of treatment failures, around 125,000 deaths, and up to 25% of hospitalizations each year in the United States. Estimates are that approximately 125,000 deaths per year in the United States are due to medication nonadherence and that 33% to 69% of medication-related hospital admissions are due to poor adherence. Although, adherence rates of 80% are recommended for optimal therapeutic efficacy, estimates place adherence to chronic medications is around 50%.[62] "The pain of preventable deaths and the personal costs of nonadherence are borne disproportionately by Black, Latino, and other minority groups because nonadherence is higher in these groups due to a variety of factors", among them socioeconomic challenges.[63]

Inadequate treatment adherence as a contributor to poor health has been recognized since antiquity. Hippocrates warned physicians that patients might "lie about the taking of things prescribed" and "… through not taking disagreeable drinks, purgative or other, they sometimes die."[64] More recently, the importance of patient compliance on health outcomes has become clear. A 2002 review declared that, "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments".[65] And, the World Health Organization declared medication adherence an issue of global importance, rallying policymakers and healthcare providers to improve public health through effective adherence support.[66]

Importance of Patents to Therapeutic Alternatives

Given the numerous advantages of having a variety of therapeutic options, the risks of failing to protect follow-on innovation are significant. The absence of patent protection for follow-on innovations could lead to several detrimental consequences for drug development and patient access. First among them, reduced investment in research and development focused on improving existing drugs. Without the potential for market exclusivity offered by patents, biopharmaceutical companies would likely devote less time, talent, and financial resources to the process of developing enhanced formulations, new delivery methods, or exploring novel uses for already approved compounds. The result could be slower development of patient-friendly formulations and delivery methods that are crucial for enhancing treatment adherence and improving patients' overall quality of life. The incentive to explore new therapeutic applications for existing drugs would also be reduced, allowing the evolution of therapeutic options to stagnate, thereby restricting the options available to clinicians and patients. Disadvantaged and vulnerable populations would be disproportionally affected.

V. BEYOND DELIVERING EQUITY, FOLLOW-ON INNOVATIONS ARE EFFICIENT

At its core, all innovation is valuable to patients, whether in the form of moving the needle a tiny bit, or breakthrough discoveries. Importantly, they address the challenges of the wider healthcare system as well. Investments in continuing innovation are economically efficient and represent prudent use of scarce resources. Ensuring that we extract the most value from investments in research and development programs makes both scientific and economic sense, exploiting the full potential of clinical trial data

which is both expensive and difficult to collect.[67] Practically, it makes sense to use science to its utmost to exploit moieties, molecules and medicines that are known to be safe and effective in another setting.

Follow-on innovation that utilizes an existing drug for a new use or new indication derisks clinical trials since the drug's safety has been established.[68] Early in the development process it is cost-prohibitive to explore multiple indications. Estimates suggest that the development of a new use for an existing drug costs between $100 and $300 million dollars.[69] Moreover, FDA approval rates of repurposed drugs near 30 percent relative to less than ten percent for new molecular entities.[70] "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".[71]

Subsequent Indications

Accordingly, the exploration of subsequent indications frequently happens after a drug's first FDA approval. A 2024 study of oncology drugs found that between 2008 and 2018, 65% of oncology drugs were developed, post-approval for at least one subsequent indication for a different type of cancer.[72] Hult finds that follow-on innovation, new drugs created by modifying existing FDA-approved molecules, accounts for 49% of the health impact of new innovations".[73]

Follow-on innovation is not only economically judicious, but therapeutically beneficial as well. The majority of therapies currently in use are incremental innovations. As evidence of the therapeutic value of follow-on drugs, a study of the World Health Organization's Essential Drug List finds that 63% of the drugs on the Lists are follow-on drugs. An earlier study found that more than 11% of the drugs on the WHO's Essential Drug List were listed for more than one indication.[74] DiMasi and Paquette (2004) provide significant evidence of the concurrent nature of the research programs that lead to the development of many follow-on drugs. In addition, the potential for patent protection incentivizes research into combining existing active ingredients, which can lead to synergistic effects and improved treatment outcomes for complex diseases.

While critics contend that profit motivates the development of imitation versions as firms race to get their me-too drugs to market, test data indicates that these research programs are better described as parallel drug development.[75] Ultimately, "[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".[76] Fundamentally, it is less costly to engage in continuing innovation, than to embark upon a new research program, with potentially superior therapeutic properties as well.

VI. RECOMMENDATIONS

Equitable access to medicines expands when a variety of treatments options are available, including specialized versions for vulnerable populations and affordable generics. Admittedly there is room for improvement and a critical need for expanding access to medicine, including to children, geriatric patients, and those in resource-limited settings. In pursuit of enhanced access, evidence-based policymaking is essential in patent law, innovation policy, and healthcare policy. The USPTO Study[77] should become the template for careful and precise analysis in the legal and policy debates concerning drug patents and drug pricing.

Specifically, the debate over follow-on innovation should be based in precise language, empirical evidence, rigorous analysis, and logically sound conclusions. As described by Erika Lietzan, "policymaking should be based on descriptive scholarship that is careful and precise about the relevant law and facts, normative work that is clear and candid about its claim and thorough in its reasoning, and

empirical studies that document the actual problem the normative proposals and policymaking proposals are meant to address".[78]

Instead, many recent proposals are based on supposition and a collection of anecdotes. Those that promote radical change demand close examination. Lietzan's work describes the normative claim at the heart of the proposals to limit patents in the biopharmaceutical industry, which "would be something like this: an innovator should not enjoy an exclusive market and supra-competitive pricing for innovations that stem in some fashion from a separate innovation for which it already enjoyed a 20-year patent term. Or at least, a drug innovator should not."[79]

From an economic perspective, a sound patent policy recognizes that patents are a solution to a market failure: too little investment if replication is easy. Patents should drive innovation, bringing society new goods and services, improvements in quality and lower prices. Finally, the best evidence of the effectiveness of the patent system should be related to innovation. Medical progress should be the yardstick. The iterative nature of biopharmaceutical innovation ensures that first-in-class innovations are improved upon through continuing innovation, a process that results in a variety of therapeutic options for patients. These improvements should be rewarded and the investments that generate follow-on innovations must be incentivized. Empirical evidence establishes that innovation happens where the legal and regulatory mechanisms protect innovation.

VII. CONCLUSION

Equitable access is enhanced when a variety of treatments are available, including affordable generic copies and specialized versions for vulnerable populations. These are treatments that have been incentivized by a legal framework, encompassing patents and other forms of market exclusivities, which encourages innovation and facilitates entry by generic and biosimilar firms. This innovative ecosystem supports innovative firms as well as generic manufacturers, ensuring a thriving U.S. biopharmaceutical industry producing innovative therapies as well as affordable versions after patent expiry.

This system incentivizes both first-in-class drugs and the continuing innovation that ensures the diffusion of improvements in safety and efficacy in follow-on versions. Without patents and other forms of IP protection, we would not have these treatments and cures. While these advances improve and extend our lives, they also ensure that there is greater equity in access to medicines.

Empirical studies establish that the pharmaceutical industry does a great deal of incremental innovation, developing new medicines that relate to, and build on, their initial discovery of a biologically useful molecule.[80] In fact, iterative improvements are "the predominant mechanism of innovation and product development within most manufacturing and high-technology industries," and are not unique to the pharmaceutical industry. [81] Incremental innovation is identified by critics as a barrier to access based in "trivial" or "frivolous" changes and labeled as the culprit responsible for delayed generic entry and high drug prices.[82] In reality, these innovations fundamentally improve equitable access to medicines for underserved populations. To enjoy these benefits, the innovation that makes them possible must be incentivized. Since pharmaceutical research and development is difficult, expensive, and risky, intellectual property rights protections are essential, and they take the form of patents and exclusivities. These protections do not represent a strategy aimed at gaming the system, rather they are at the heart of the system that transforms ideas into treatments and cures.

The ultimate promise of innovation is fulfilled when generic versions of medicines become available. Generic drugs provide society with trillions of dollars in savings, as intended by the patent system. Expiring patents motivate researchers and investors to explore new opportunities, expanding the variety of therapeutic options available, valuable options especially for vulnerable and disadvantaged

populations. Undermining innovation won't provide equity in access, except to the extent that it ensures that medicines aren't developed and no one has access. Given this, policy proposals advocating radical change should be approached warily, and all recommendations should be based in empirical data and rigorous analysis.

Follow-on innovations generate benefits for individual patients, public health, the healthcare system, and the overall economy. Work on incremental innovations is the source of most medical progress, and broadens the reach of new drugs to a diversity of populations. To ensure equity in access, access for more people to more treatments and cures, more innovation is needed, not less.

ENDNOTES

[1] National Research Council (1996). *Prospectus for National Knowledge Assessment.* National Academy Press, as cited in Wertheimer, Albert I., and Thomas M. Santella (2005). *Pharmacoevolution: the Advantages of Incremental Innovation*. IPN Working Papers on Intellectual Property, Innovation and Health. International Policy Network, pg.6.
[2] Lybecker, Kristina M. "Incremental Innovation in the Pharmaceutical Industry," Fraser Institute, Vancouver, BC, Canada, June 2014, https://www.fraserinstitute.org/sites/default/files/benefits-of-incremental-innovation.pdf.
[3] Consider the following sample of studies reviewing follow-on innovation.

- Barbosu, Sandra. "The Value of Follow-on Biopharma Innovation for Health Outcomes and Economic Growth," Information Technology and Innovation Foundation (ITIF), March 2025, https://itif.org/publications/2025/03/17/the-value-of-follow-on-biopharma-innovation/
- Berndt, Ernst R., Iain M. Cockburn, and Karen A. Grepin. "The impact of incremental innovation in biopharmaceuticals: drug utilisation in original and supplemental indications." Pharmacoeconomics 24.Suppl 2 (2006): 69-86.
- Cohen, Joshua, and Kenneth Kaitin. "Follow-on drugs and indications: the importance of incremental innovation to medical practice." American journal of therapeutics 15.1 (2008): 89-91. https://journals.lww.com/americantherapeutics/citation/2008/01000/follow_on_drugs_and_indications__the_importance_of.15.aspx
- Holman, Christopher M. "In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination", 50 Indiana Law Review 759 (2017).
- Holman, Christopher M., Timo Minssen, and Eric Solovy, Patentability Standards for Follow-on Pharmaceutical Innovation, 37 Biotechnology Law Report 131 (2018).
- Hult, Kristopher J. Incremental innovation and pharmaceutical productivity. Diss. The University of Chicago, 2015. https://www.proquest.com/openview/103a0fd49f86a33727eadebc6cc06593/1?pq-origsite=gscholar&cbl=18750
- Lanthier, Michael L.,Kirk W. Kerr, and Kathleen L. Miller. "An Analysis of Follow-on Development in New Drug Classes, January 1986-June 2018," Clinical Pharmacology Therapy, 2019 July 26, vol.106, no.5, pp.1125-1132. https://pmc.ncbi.nlm.nih.gov/articles/PMC8422864/
- Lybecker, Kristina M. "Incremental Innovation in the Pharmaceutical Industry," Fraser Institute, Vancouver, BC, Canada, June 2014, https://www.fraserinstitute.org/sites/default/files/benefits-of-incremental-innovation.pdf.
- Okuyama, Ryo. "Importance of tacit knowledge in incremental innovation: Implications from drug discovery cases." Journal of Strategy and Management 10.1 (2017): 118-130.
- Wertheimer, Albert I., and Thomas M. Santella. "Pharmacoevolution: the advantages of incremental innovation." International Policy Network2009 (2004).
- Wertheimer, Albert I., Thomas M. Santella, and Nicole M. Chaney. "The World Health Organization's Essential Medicines List: An Endorsement of Incremental Innovation and Follow-On Research." Journal of Pharmaceutical Marketing & Management 17.2 (2005): 25-34. https://www.tandfonline.com/doi/abs/10.3109/J058v17n02_04
- Wertheimer, Albert, Richard Levy, and Thomas O'Connor. "Too many drugs? The clinical and economic value of incremental innovations." Investing in health: the social and economic benefits of health care innovation. Emerald Group Publishing Limited, 2001. 77-118.

[4] I-MAK Mission Statement, https://www.i-mak.org/mission/.
[5] Lietzan, Erika. "The 'Evergreening' Metaphor in Intellectual Property Scholarship", 53 *Akron Law Review* 805, 2019, https://scholarship.law.missouri.edu/facpubs/984.
[6] IGBA, "Gaming the System," January 2025, https://www.igbamedicines.org/doc/IGBA_IP&Comp_Report-v20250123.pdf.
[7] IFPMA, "Always Innovating: Pharmaceutical Industry Facts & Figures," December 9, 2024. Available at: https://www.ifpma.org/publications/alwaysinnovating-pharmaceutical-industry-facts-figures/.
[8] Industry Critics: Doctors without Borders (MSF) argues, "Drug companies hold patents, giving them a monopoly on treatments. Drug patent systems can be manipulated and abused, limiting market competition and blocking affordable alternatives. Patent laws and regulations limit the places where urgently needed drugs can be used." https://www.doctorswithoutborders.org/what-we-do/focus/global-access-to-medicine. While I-MAK claims "Patients in Europe, Canada, Japan, and other similar markets benefit from earlier generic entry compared to patients in the U.S., who have to wait years longer for low-cost generic products. The earlier generic entry can be attributed to how these countries' patent systems are set up. This includes limiting the endless filing of continuation

patents that are used to build large patent thickets. As a result, fewer patents would be granted and available for enforcement in litigation and the extraction of settlements. (https://www.i-mak.org/overpatented/)

[9] Government Policymakers: Brachmann, Steve. "Drug Patent Thicket Letter from U.S. Senators to Vidal Seeks Reforms on Continuation Patent Filings", IPWatchdog, June 15, 2022, https://ipwatchdog.com/2022/06/15/drug-patent-thicket-letter-u-s-senators-vidalseeks-reforms-continuation-patent-filings/id=149639/. Courtenay C. Brinckerhoff, USPTO Aims to Mow Down Patent Thickets, Foley Insights (May 13, 2024), https://www.foley.com/insights/publications/2024/05/uspto-mow-down-patent-thickets/. Medication Affordability and Patent Integrity Act, S.2780 (118th Congress, 2023), https://www.congress.gov/118/bills/s2780/BILLS118s2780is.pdf. Senator Elizabeth Warren has demanded the compulsory licensing of patents for drugs. (https://www.cagw.org/sen-elizabeth-warren-wants-the-government-to-steal-ip-and-stifle-future-pharmaceutical-innovation/)

[10] Academics: Robin Feldman proposes a solution which she calls "one-and-done" arguing that "one period of protection should be enough" and thus "a drug" should "receive just one period of exclusivity, and no more". Feldman, Robin. "May Your Drug Price Be Evergreen", Journal of Law and Biosciences, vol.5, issue 3, 2018, pp.590-647, https://academic.oup.com/jlb/article/5/3/590/5232981. Feldman, Robin. "One and Done for New Drugs Could Cut Patent Thickets and Boost Generic Competition," STAT, Feb. 11, 2019, https://www.statnews.com/2019/02/11/drug-patent-protection-one-done/. Syed (2025) proposes to do away with patents in exchange for changes to exclusivity protections. Syed, Talha. "Does Pharma Need Patents?" The Yale Law Journal, vol.134, no.6, April 2025, https://www.yalelawjournal.org/feature/does-pharma-need-patents.

[11] https://www.wto.org/english/tratop_e/trips_e/pharmpatent_e.htm

[12] USPTO, "Drug Patent and Exclusivity Study," June 2024, https://www.uspto.gov/initiatives/fda-collaboration/drug-patent-andexclusivity-study-available. [hereafter: "USPTO Study"]

[13] Wertheimer, et al. (2001), supra note 3.

[14] Lybecker (2014), supra note 3.

[15] Frank, Richard G. "The Ongoing Regulation of Generic Drugs," *The New England Journal of Medicine*, vol.357, no.20, 2007, https://www.nejm.org/doi/10.1056/NEJMp078193.

[16] "Office of Generic Drugs 2022 Annual Report," FDA (2022), https://www.fda.gov/drugs/generic-drugs/office-generic-drugs-2022-annual-report.

[17] Barbosu, Sandra. "The Value of Follow-on Biopharma Innovation for Health Outcomes and Economic Growth," Information Technology and Innovation Foundation (ITIF), March 2025, https://itif.org/publications/2025/03/17/the-value-of-follow-on-biopharma-innovation/

[18] Acri, Kristina M.L. "Regulatory Exclusivities in the Biopharmaceutical Ecosystem," working paper, June 2, 2025. Forthcoming in Bringing Medicines to Life: How Intellectual Property Enables Innovation in the Life Sciences (eds. Jonathan M. Barnett and Bowman Heiden, Cambridge University Press, forthcoming 2026). Working paper currently available on SSRN: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5363518.

[19] C4IP, "Debunking Patent Disinformation: Insights from the USPTO's Drug Patent and Exclusivity Study," January 2025, https://c4ip.org/debunking-patent-disinformation-insights-from-the-usptos-drug-patent-and-exclusivity-study/

[20] Autism Therapy Services, "U.S. Pharmaceutical Statistics," online post, 2025, available at: https://www.yellowbusaba.com/post/u-s-pharmaceutical-statistics.

[21] 35 U.S.C. § 101(emphasis added).

[22] Lietzan, Erika. "The 'Evergreening' Metaphor in Intellectual Property Scholarship", 53 *Akron Law Review* 805, 2019, at p.6, https://scholarship.law.missouri.edu/facpubs/984.

[23] *Ibid.*

[24] Winegarden, Wayne. "The Economics of Pharmaceutical Pricing," Pacific Research Institute, June 2014, www.pacificresearch.org/wp-content/uploads/2017/06/PhamaPricingF.pdf

[25] Vernon, J.A., J.H. Golec, and J.A. DiMasi. "Drug Development Costs When Financial Risk is Measured Using the Fama-French Three-Factor Model," Health Economics, 2010, vol.19, no.8, pp. 1002-1005.

[26] Acri (2025), supra note 16, 14. The sources of these numbers are:

(a) Canadian Intellectual Property Council (CIPC). Innovation for a Better Tomorrow: Closing Canada's Intellectual Property Gap in the Pharmaceutical Sector, January 2011, at p.12. http://www.ipcouncil.ca/uploads/Innovation%20for%20a%20Better%20Tomorrow.pdf

(b) Sertkaya, Aylin, Andreas Lord and Clara Berger. "Cost of Generic Drug Development and Approval," Eastern Research Group, Inc. Report Submitted to U.S. Department of Health and Human Services, Office of the Assistant Secretary of Planning and Evaluation, December 31, 2021. https://aspe.hhs.gov/sites/default/files/documents/20e14b66420440b9e726c61d281cc5a5/cost-of-generic-drugs-erg.pdf

(c) Drug Patent Watch. "Understanding the Lifecycle of Generic Drugs: From Development to market Impact," online post, 6 December 2024. https://www.drugpatentwatch.com/blog/understanding-the-lifecycle-of-generic-drugs-from-development-to-market-impact/
(d) Government Accountability Office (GAO). "Generic Drug Applications: FDA Should Take Additional Steps to Address Factors that May Affect Approval Rates in the First Review Cycle," GA-19-565, August 2019. https://www.gao.gov/assets/gao-19-565.pdf
(e) U.S. Food and Drug Administration. "The Drug Development Process," online post, January 2018. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process
(f) Stroebel, Hettie. "10 tips for improved drug development," Pharma Manufacturing, online post, 14 June 2022. https://www.pharmamanufacturing.com/development/process-development/article/11287499/10-tips-for-improved-drug-development
(g) Please see the list of references cited in Acri (2025), supra note 16, 15.
(h) Please see the list of references cited in Acri (2025), supra not 16, 7.
(i) This calculation is derived by subtracting the years spent "Time from Laboratory to Market" from the 20-year patent life.

[27] Association for Accessible Medicines. "2024 U.S. Generic & Biosimilar Medicines Savings Report," online post, 2025, http://www.accessiblemeds.org/resources/reports/2024-savings-report/.

[28] Barei, Fereshteh, Claude Le Pen and Steven Simoens. "The generic pharmaceutical industry: moving beyond incremental innovation towards re-innovation," Generics and Biosimilars Initiative Journal, vol.2, no.1, 2013, pp.13-19. https://gabi-journal-net.server1.ech.be/wp-content/uploads/GJ-2013-1-p13-19-OriginalResearch-Barei.pdf

[29] World Intellectual Property Organization (WIPO) "Patent Landscape Report on Ritonavir," 2011, at 31. https://www.wipo.int/publications/en/details.jsp?id=230. [hereafter: "WIPO Analysis"]

[30] https://www.fda.gov/drugs/cder-conversations/40th-anniversary-generic-drug-approval-pathway.

[31] https://www.fda.gov/drugs/biosimilars/biological-product-innovation-and-competition.

[32] *Id.* Lietzan (2019) does an excellent job cataloguing the claims and categorizing them. These claims are frequently made by critics of the biopharmaceutical industry. Please see notes 4, 6, 8-10.

[33] Lietzan, Erika. "The Evergreening Myth," *Regulation*, Fall 2020, pp.24-29, https://www.cato.org/regulation/fall-2020/evergreening-myth#.

[34] Lietzan (2019), supra note 19, at 49-52.

[35] USPTO Study, supra note 12, at 69.

[36] USPTO Study, supra note 12. In addition, in a 2023 study by Lietzan and Acri, the authors study the average market exclusivity periods for 225 new drug applications at the FDA, finding the average length of time before generic entry to be only 11.3 years. Lietzan, Erika and Kristina M.L. Acri née Lybecker, "Solutions Still Searching for a Problem: A Call for Relevant Data to Support 'Evergreening' Allegations", 33 Fordham Intellectual Property, Media and Entertainment Law Journal, 788 (2023), https://ir.lawnet.fordham.edu/iplj/vol33/iss4/2/. A previous study by Lietzan and Acri examining 227 drugs that had received patent term extensions under the patent laws between 1984 and 2018 found an average period of market exclusivity of only 12.62 years. Lietzan, Erika and Kristina M.L. Acri née Lybecker. "Distorted Drug Patents", 95 *Washington Law Review*, 1317, 1326-29 (2020), https://digitalcommons.law.uw.edu/wlr/vol95/iss3/6/.

[37] USPTO Study, supra note 12.

[38] USPTO Study, supra note 12.

[39] Lietzan (2019), supra note 19, at 53-59.

[40] USPTO Study, supra note 12, 59, noting that "patent expiration dates, like the number of patents, may not be predictive of the timing of actual launch of competing products… because not all listed patents may be infringed by a generic product".

[41] *Ibid.*

[42] *Ibid.*

[43] Barbosu (2025), supra note 15, at 8.

[44] Wastilla, L.J., M.E. Ulcickas, and L. Lasagna. The World Health Organization's Essential Drug List. The Significance of Me-Too and Follow-On Research. *Journal of Clinical Research and Drug Development,* 1989, 3, at 105.

[45] Kapczynski, Amy. Engineered in India—Patent Law 2.0. *New England Journal of Medicine* (online edition) July 17, 2013, http://www.nejm.org/doi/full/10.1056/NEJMp1304400.

[46] Lybecker, Kristina M. Patent Law 2.0: Not the Answer the Developing World Needs. IPWatchDog, August 18, 2013, www.ipwatchdog.com/2013/08/18/patent-law-2-0-not-the-answer-the-developing-worldneeds/id=44699 /.

[47] Kyle, Margaret, and Anita M. McGahan. Investments in Pharmaceuticals before and after TRIPS. Review of Economics and Statistics 94, 4, November 2012, pp 1157–1172.

[48] Holman, C.M., et al. "Patentability Standards for Follow-On Pharmaceutical Innovation," 37 Biotechnology Law Report, 2018, 131-161, 134.
[49] Lybecker (2014), supra note 2.
[50] Aptitude Health. https://www.aptitudehealth.com/oncology-news/most-fda-and-ema-oncology-drug-approvals-in-q1-2025-were-new-indications-for-biologics-and-biosimilars/
[51] Homan, Christopher M. "Why Follow-On Pharmaceutical Innovations Should Be Eligible For Patent Protection," Intellectual Property Watch, September 2018. https://www.ip-watch.org/2018/09/21/follow-pharmaceutical-innovations-eligible-patent-protection/
[52] *Ibid.*
[53] Lybecker (2014), supra note 2, describes more than 20 examples in addition to those listed here.
[54] Barbosu (2025), supra note 15, at 4.
[55] Wong, D., et al. (2005) "The Discovery of Fluoxetine Hydrochloride (Prozac)." Nature Reviews Drug Discovery, 4: 764-774. https://www.nature.com/articles/nrd1821
[56] Patchett AA, Harris E, Tristram EW et al. (1980) A new class of angiotensin-converting enzyme inhibitors. Nature 288 (5788): 280–3.
[57] Minze, Molly G., Mary S. Klein, and Brian T. Terrell. "Saxagliptin and Metformin in Fixed Combination for the Treatment of Type 2 Diabetes in Adults," Clinical Medicine Insights: Endocrinology and Diabetes, July 31, 2013, 6, pp.15-24. https://pmc.ncbi.nlm.nih.gov/articles/PMC3738378/
[58] Barei, Le Pen and Simoens, (2013), supra note 28.
[59] Sabaté E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization. 2003. www.who.int/chp/knowledge/publications/adherence_report/en/ ; DiMatteo MR, Giordani PJ, Lepper HS, et al. Patient adherence and medical treatment outcomes: a meta-analysis. Med Care. 2002;40(9):794-811.
[60] Benjamin, Regina M. "Medication Adherence: Helping Patients Take Their Medicines as Directed," Public Health Reports, 2012 Jan-Feb, vol.127, no.1, pp.2-3, https://pmc.ncbi.nlm.nih.gov/articles/PMC3234383/
[61] NEHI (New England Health Care Institute) 2009. Aug 12. Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease. http://www.nehi.net/publications/44/-thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease
[62] DiMatteo et al. (2002), supra note 58.
[63] Ding, Alexander, Suzanne W Dixon, Erin A Ferries, and William H Shrank. "The role of integrated medical and prescription drug plans in addressing racial and ethnic disparities in medication adherence," J Manag Care Spec Pharm. 2022;28(3):379-86 https://www.jmcp.org/doi/10.18553/jmcp.2022.28.3.379
[64] Haynes RB. Chapter 1: introduction. In: Haynes RB, Taylor DW, Sackett DL, eds. Compliance in Health Care. The John Hopkins University Press; 1979:1-7. Wright, Daniel F.B., Klarissa A. Sinnappah, and Dyfrig A. Hughes. "Medication Adherence Research Comes of Age," British Journal of Clinical Pharmacology, July 2023, vol.89, no.7, pp.1914-1917, https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15722
[65] The Cochrane Collaboration, Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002;(2):CD000011.
[66] World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. World Health Organization; 2003. https://apps.who.int/iris/handle/10665/42682
[67] For new molecules, the clinical portion of an R&D program averages six years. Lietzan (2020), supra note 20, at 24.
[68] Tudor I. Oprea and J. Mestres, "Drug repurposing: far beyond new targets for old drugs," The AAPS Journal Vol. 14 (2012): 759–763.
[69] Lietzan, E. (2018) "Paper Promises for Drug Innovation," George Mason Law Rev. 26: 168-214, at 177.
[70] Barbosu (2025), supra note 15, at 7, citing J. J. Hernandez et al., "Giving drugs a second chance: overcoming regulatory and financial hurdles in repurposing approved drugs as cancer therapeutics," Frontiers in Oncology Vol. 7, No. 273 (2017); Pinzi et al., "How drug repurposing can advance drug discovery: challenges and opportunities."
[71] Barbosu (2025), supra note 15, at 6, citing Sudeep Pushpakom et al., "Drug repurposing: progress, challenges and recommendations," Nature Reviews Drug Discovery Vol. 18, No. 1 (2019): 41–58.
[72] Patterson, j. et al., "Subsequent Indications in Oncology Drugs: Pathways, Timelines, and the Inflation Reduction Act," Therapeutic Innovation & Regulatory Science (2024): 1–10.
[73] Hult (2015), supra note 3.
[74] Wertheimer, Santella, and Chaney (2005), supra note 3.
[75] DiMasi, Joseph A., and Cherie Paquette (2004). The Economics of Follow-on Drug Research and Development. Pharmacoeconomics 22, supplement 2: 1–14.
[76] Lybecker (2014), supra note 2.

[77] USPTO Study, supra note 12.
[78] Lietzan (2019), supra note 20, at 5.
[79] Lietzan (2020), supra note 5, at 5.
[80] Lietzan (2020), supra note 5, at 48.
[81] Wertheimer, et al. (2001), supra note 3, at 78.
[82] For example: Lemley, Mark A. "Expecting the Unexpected," *Notre Dame Law Review*, vol.92, 2017, 1369; Lim, Daryl. "Self-Replicating Technologies and the Challenge for the Patent and Antitrust Laws," Cardozo Arts and Entertainment Law Journal, vol.32, 2013; and Reichman, Jerome H. "Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case for A Public Goods Approach," Marquette Intellectual Property Law Review, 2009, vol.13, pp.1-68.