HEALTH & MEDICINE

The Evergreening Myth

Claims that drug innovators extend their patents obscure a radical policymaking goal.

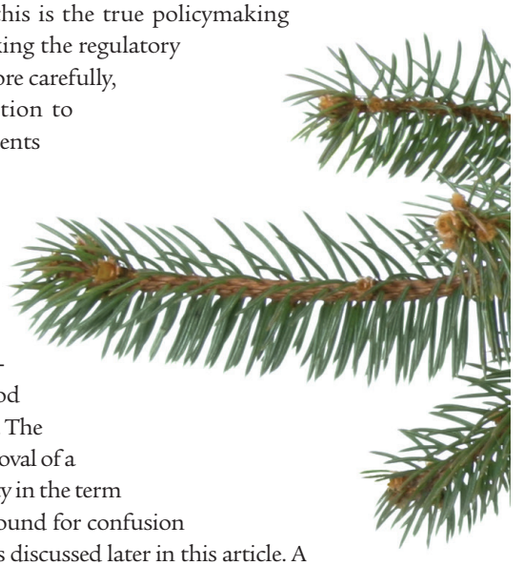
BY ERIKA LIETZAN

In recent years, U.S. policymakers have considered proposals intended to prevent—or at least reduce—"evergreening" by pharmaceutical companies. Some proposals would change the antitrust enforcement landscape, others the intellectual property landscape, and still others the regulatory framework that governs new medicines. Some proposals—such as those creating new causes of action under the antitrust laws or limiting the availability of patents for discoveries—are profound and their proponents cite a body of academic and policy literature that decries supposed "evergreening" by companies to justify their ideas.

The term "evergreening" is a metaphor, meant to remind audiences of evergreen trees, which have green foliage year-round. It implies that something has been extended, and users of the metaphor view this extension as improper or undesirable. When offering descriptions and examples of evergreening, they focus on drug companies continuing to innovate after first introducing a new molecule, and on the broader marketplace for medicines after subsequent innovations have been introduced to the market. But proponents are frustratingly inconsistent and unclear about what, exactly, has been "extended" in these situations. A close look at the regulatory landscape in which continuing pharmaceutical innovation occurs shows that arguments for reform are grounded in myths, such as the myth that pharmaceutical companies continuing to innovate somehow "extend" their patents.

Once the myths of "evergreening" are laid bare, it becomes apparent that proponents of these proposals really want for the government to limit medical innovators to one medical product in the marketplace for each useful new molecule discovered. They are arguing that an innovator should not enjoy an exclusive market—and the resulting advantageous pricing—for innovations that, though discrete and independently satisfying the standard for a patent under U.S. law, stem in some fashion from an earlier innovation for which that innovator *separately* enjoyed exclusivity and the resulting pricing advantages. Or, at least, that drug innovators should not. This is a radical proposal that merits careful reflection and discussion, and it is not ripe for action.

Understanding that this is the true policymaking objective requires unpacking the regulatory landscape and market more carefully, and paying closer attention to word choice, than proponents of reform often do.



THE EVERGREENING ALLEGATION

In the United States, every new medicinal product requires premarket approval from the Food and Drug Administration. The drug statute refers to approval of a "new drug," and ambiguity in the term "drug" provides fertile ground for confusion and rhetorical mischief, as discussed later in this article. A firm that wants to market a new drug must prove to the FDA that the drug is safe and effective. Generating this information takes years, beginning with work in the laboratory and on animals, and progressing through several rounds of "clinical" testing in humans. For new molecules, the clinical portion of this research and development program averages six years. The process is also expensive: the Tufts Center for the Study of Drug Development now estimates the average cost of developing a new molecular entity at $2.6 billion. That figure includes average out-of-pocket costs of $1.4 billion and reflects the cost of unsuccessful projects. Most research and development programs fail.

When new drugs are first launched by innovators, they tend to be sold under brand names and protected by patents as well as statutory rights in the data that supported FDA approval (known as "data exclusivity"). Although the pricing of these products may reflect competitive pressure from other branded products, it also

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reflects the fact that patent rights and statutory data exclusivity delay the launch of cheaper copies. But no more than five years later, and often earlier, the innovator's competitors may file applications seeking approval of their own products based on the *innovator's* research, rather than performing their own. They file what are known as "abbreviated applications"—abbreviated because they omit some, or all, of the research needed to prove safety and effectiveness. Abbreviated applications are much less expensive and time-consuming to assemble, and the competitors' drugs correspondingly much less expensive than the original drugs they copy. When a competitor seeks to market an exact copy through an abbreviated application, we call its drug a "generic" drug. Pharmacists usually dispense generic copies even when doctors prescribe the corresponding branded products by name.

VIKTOR_KITAYKIN / GETTY IMAGES (BRANCH); SMARTSTOCK / ISTOCK / GETTY IMAGES PLUS (PILL BOTTLE)

Some people use the "evergreening" label when an innovator holds more than one patent protecting its product, especially if some patents expire later than others. More often, though, these people use the label when an innovator introduces a newer version of its own product that is already on the market. These newer products tend to be sold under brand names and protected by their own patents and statutory data exclusivity. Sometimes the innovator also stops selling its older product. If purchasers shift to the innovator's newer product rather than purchasing cheap copies of the innovator's older product, some say the innovator has engaged in evergreening.

Although the term "evergreening" is a metaphor and signifies an extension of something, proponents of reform proposals do not agree on the particulars of the term's use. Some say the company has evergreened its invention, its drug, or its product. Others say the company has evergreened the drug's patent or patent life, or its exclusivity. Some say it has extended the drug's patents, or the drug's patent coverage or patent life, or the drug's exclusivity period. Some say the company has evergreened the drug's price, or its own profits or monopoly, or the company has extended its market power. Many argue that through evergreening—whatever the term means—the innovator has improperly blocked other firms from competing with it. On this basis, they seek government intervention. For instance, one recent proposal would allow the Federal Trade Commission to bring antitrust actions against innovators who introduced newer products to replace their older products.

THREE MYTHS OF EVERGREENING

The circumstances that trigger the "evergreening" label occur at the intersection of several complex bodies of law: 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 medicines. Many who propose aggressive government intervention because of evergreening give short shrift to this landscape, which allows the perpetuation of three myths that distort policymaking discussions.

Before reviewing the myths, it will help to understand two points about the framework in which innovators compete with the companies that submit abbreviated applications. First, the FDA approves *products*, not active ingredients. And second, patents protect *inventions*, not products.

Federal law states that every "new drug" requires an approved application. But at the FDA the term "drug" has more than one meaning. It includes a medicine's active ingredient, to be sure. But it also includes drug *products*. A drug product is a medicine in its finished form, meaning the form that will be sold in the market and administered to patients. And the FDA approves a particular product described in a particular application—the specific combination of active and inactive ingredients (often called a drug's "formulation"), in a particular dosage form (such as capsule or tablet), for a particular route of administration (such as oral or topical), at a particular strength, for particular medical uses (also known as the product's "indications"), manufactured as described in the application, and accompanied by labeling written for prescribers based on the data in the application.

Federal law allows a patent to issue for any new, useful, non-obvious invention, including a process, a composition of matter, and an improvement to an existing process or composition of matter. The patent usually expires 20 years after its application date. For any particular drug *product* approved by the FDA, the innovator might own patents on various types of inventions. The innovator usually owns a patent claiming the product's active ingredient, and because the innovator generally files this patent before starting clinical trials, it is usually the first to expire. Other inventions protected by patent might include the product's formulation or a dosage form and dosage of the active ingredient (or formulation). These inventions may emerge later in the premarket development process. If the resulting patent applications refer to the active ingredient patent, the patents will expire when the active ingredient patent expires, but otherwise they will expire later. The innovator may also own other patents claiming inventions embodied in the product, such as a patent claiming methods of using or administering the product, a patent claiming the manufacturing process, or a patent claiming a metabolite of the active ingredient. These, too, could expire later than the first patent—sometimes much later.

These two points work together. A single active ingredient associated with a single brand name might be the subject of a half dozen, dozen, or more discrete products. Suppose an active ingredient was formulated into tablets and the innovator sold six strengths. Suppose the innovator also formulated an injectable version, which it sold in two strengths. Suppose it also developed a disintegrating tablet for oral administration, which it sold in four strengths. This innovator would sell *12 discrete products* with the same active ingredient and probably (though not necessarily) the same brand name. And because a single product might incorporate many discrete inventions, the patents relevant to one product might differ from the patents relevant to another. Failure to realize this—and its regulatory significance—leads to three myths, as follows.

Myth of evergreening patents / The first myth is that innovators extend their patents. This is legally impossible. In the United States, a patent expires 20 years after its application date.

There are only two ways a patent's expiration date can shift later in time: (1) When it issues a patent, the U.S. Patent and Trademark Office (PTO) adjusts the expiry date later to compensate for routine delays at the PTO. And (2), if the marketing application proposed a new active ingredient, then if the company asks the PTO for a patent term extension within 60 days of FDA approval, the PTO will use a statutory formula to extend one patent claiming the product to compensate partially for the lapse of patent life during premarket testing and regulatory review. There is no other mechanism by which a patent might be extended. In particular, a patent on one invention—no matter when it expires—does not extend the patent on another invention.

Myth of blocked competitors / The second myth is that when an innovator holds patents that expire after its active ingredient patent, or when it introduces newer products to market, it can prevent its competitors from bringing their copies to market. Instead, once the initial patent and (if applicable) statutory exclusivity on the innovator's active ingredient have expired, its competitors have substantial freedom to operate. This freedom reflects two facts that are often overlooked.

First, the innovator's competitor does not have to propose an exact copy. Federal law permits the competitor to rely on the innovator's research but propose competing products that are *not* identical. To be sure, a competitor may submit an ANDA for a product that essentially duplicates the innovator's product—that is, a generic. Ordinarily, the company shows in the ANDA that its product has the same active ingredient, route of administration, dosage form, strength, and labeling as the innovator's product. The generic must also be "bioequivalent" to the original drug that it references, meaning that its active ingredient must reach the site of action in the body to the same extent and at the same rate as the active ingredient of the referenced product. But even a generic can be a little different. For example, it usually does not need the same inactive ingredients in the same quantities. And the generic competitor need not use the same manufacturing process.

If a competitor wants to offer a different route of administration, dosage form, or strength—for instance, to avoid infringing a patent—it may still be able to use the generic drug approval pathway. It simply files a "suitability petition" asking the FDA's

permission. The agency will approve the petition unless more data are needed to establish the proposed product's safety and effectiveness. And at this point, the competitor may file an ANDA. More significantly, though, a competitor can always use a *different* abbreviated application pathway: a "505(b)(2)" application for a product that differs more substantially from the innovator's product. Although the changes proposed in this hybrid application must be supported by new data, the competitor otherwise relies on the innovator's data, avoiding the expensive and time-consuming research and development process the innovator went through. In addition to using this mechanism to propose modifications that avoid a patent, a competitor might use the mechanism to propose innovations that will offer an advantage in the market—such as changes to the active ingredient and new medical uses.

Second, an abbreviated application cites a specific innovative product, not the active ingredient or brand writ large. The competitor selects *one* innovative product as the reference product on which it relies—for instance, one of the 12 products in the hypothetical above. Its regulatory burden is tied to that specific product alone. The requirement to show sameness and bioequivalence (for an ANDA) and, critically, the obligation to contend with patents and wait for statutory exclusivity to expire are linked to the one specific product, alone. (In rare circumstances, when filing a hybrid application, a competitor might cite two innovative products, but the same point applies.)

To be sure, the patents associated with the cited innovative product affect when the FDA may approve the abbreviated application. Whether it files an ANDA or a hybrid application, a competitor must address the unexpired patents listed in the FDA's "Orange Book" for the specific innovative product it has chosen to cite. For each listed patent, it has two choices, and its selection dictates the timing of FDA approval as far as that patent is concerned. The competitor may state the date on which the patent will expire, signaling that it does not plan to market its product until expiry. This precludes final approval of its product until patent expiry. Or it may assert that the patent is invalid or will not be infringed by its product, notifying the innovator of this position. If the innovator sues within 45 days, the drug statute stays final approval of its abbreviated application for 30 months. Under changes to the law made in 2003, though, unless the competitor changes its position on a patent *after* filing its abbreviated application, approval of its application is stayed only once. At the end of the 30 months, the FDA must approve the abbreviated application if the approval standard is met, even if there is ongoing patent litigation.

Although a competitor using the abbreviated application pathway must contend with the innovator's patents and approval of its product may be delayed because of those patents, this is true of *only* the patents associated with the specific product that it references. The competitor does not have to contend with patents associated with other products that happen to contain the same active ingredient or bear the same brand name. Similarly, the competing applicant grapples with only the statutory exclusivity associated with the product it references. The drug statute provides five years of exclusivity in the data supporting new chemical entities and three years of exclusivity for most new products that are not new chemical entities. Separately, if an innovator introduces what the FDA calls a new "condition of approval"—such as a new strength or dosage form—the drug statute may provide three years of exclusivity. This delays approval of abbreviated applications proposing products with the same active ingredient for the same condition of approval. But a competitor that proposed a different strength or dosage form—or that cited a product with a different strength or dosage form (such as the innovator's original product)—would not need to grapple with that exclusivity.

This debunks the myth that an innovator with later-expiring patents and an innovator that introduces newer products can prevent its competitors from bringing copies to market. Instead, competitors have several options. For instance, empirical studies show that competitors file abbreviated applications as early as the law permits them to do so, arguing that the innovator's patents are invalid or, if applicable, not infringed by the new drug. They tend to lose these arguments when the active ingredient patent is at issue, but they tend to win if a formulation patent is at issue. If a competitor believed it would infringe a patent or feared it would lose the patent infringement suit brought by the innovator, it could seek a license. Settlements of patent litigation between innovators and competitors seeking to market generic copies usually include a license allowing the competitor to bring its product to market earlier than the date of patent expiry. There are also other options.

Once the patent on the active ingredient expires, a competitor can use the ingredient in its own product and file an abbreviated application, relying on the research performed and submitted by the innovator. Even in an ANDA, a true generic application, only the active ingredient must be the same. A competitor may be able to design around patents claiming other aspects of the innovator's product (such as its strength and route of administration) and *still* file a true generic application. The competitor would simply file a suitability petition and, upon approval of that petition, a generic application proposing the difference that allowed it to avoid patent infringement. Then it would assert non-infringement in its application. If it could not file a generic application (for instance, because the FDA requested data to support the changes made), it could always file a hybrid application. It would still rely on the innovator's research and it would similarly assert non-infringement in its application. In either case, the innovator might not sue if the competitor clearly avoided its patents.

It is thus misleading for advocates of intervention to complain about the number of "patents" associated with a "drug." A competitor filing an abbreviated application does not copy a "drug" in the broad sense of the term. Accurately describing a company's freedom to operate in the market would require focusing on *discrete products* that can serve as references for abbreviated applications and on the number, scope, and breadth of the patent *claims* held by the innovator for *those products*. This would tell policymakers more about the

market effects of a firm's innovation and patenting practices than the number of patents associated with a particular brand name or the number of patents associated with the many finished products containing a particular active ingredient.

Myth that automatic substitution is critical / The final myth of evergreening is that continuing innovation—especially when an innovator introduces a newer version of its product and stops selling its old version—precludes uptake of less expensive medicines by interfering with automatic pharmacy substitution under state pharmacy law. This myth reflects an assumption that competitors who file abbreviated applications *depend* on automatic pharmacy substitution—rather than the ordinary rough and tumble of a competitive marketplace—to obtain market share. The truth may be more complicated.

Automatic pharmacy substitution arises through a combination of longstanding FDA practices and state pharmacy law. Once the agency has approved two products with the same active ingredient, it assesses whether they are "therapeutically equivalent." Designating two as therapeutically equivalent means that they have the same clinical profile and that they can be "substituted": either can be dispensed instead of the other. A true generic drug, an exact copy of the innovator's product approved based on an ANDA, will be deemed therapeutically equivalent. Every state either permits or requires pharmacists to dispense a therapeutically equivalent generic drug when a doctor prescribes an innovator's drug by its brand name, unless the doctor has said not to. The notion advanced by critics of alleged "evergreening" is that once an innovator introduces a newer version of its branded product, doctors will prescribe the newer version. And because the generic company instead copied the *older* version, pharmacists will not—cannot under state law—substitute the generic product when the patient presents a prescription for the newer innovator product.

The problem with this argument is that actual dispensing decisions probably reflect a more complex interaction of prescriber decisions, payer preferences, and state law. To begin with, a doctor may specify either branded drugs or generic drugs. A doctor could write the brand name, to be sure, but the doctor could also simply identify the active ingredient, which will usually lead the pharmacist to dispense one of the available generic drugs. In theory, the doctor could even identify a particular generic company's drug containing a particular active ingredient. And while drugmakers rarely promote generic drugs to doctors and patients, nothing prevents them from doing so. They *do* promote their therapeutically equivalent generic drugs to pharmacies and payers, focusing on the lower prices they offer. And a company that filed a hybrid application for a product that differed from the innovator's product might brand its product and promote the distinguishing features, or (depending on the reason it filed the hybrid application) position the product as a near-duplicate of the more expensive branded alternatives and promote it as such.

In short, an innovator's newer product creates a new choice for doctors and payers. To be sure, if doctors select this product, pharmacists will dispense it rather than generic copies of the innovator's older product. Doctors might shift their prescribing to the newer product for many reasons, including persuasive advertising and promotion—meaning they come to believe (based on advertising that, per FDA rules, must be truthful and not misleading) that there are benefits to the newer product. They might shift for other reasons, including experience treating patients with the two options. But companies may advertise and promote generic products to doctors and patients as well, and based on this advertising (or for other reasons, such as experience with the older innovative product that the competitor copied) doctors might *not* select the innovator's newer product. They might specify the innovator's older product (which would lead to automatic substitution, even if the innovator no longer markets the product) or, again, a generic product itself.

Generic companies will be able to introduce copies of the innovator's first product and they may or may not enjoy sales depending on the choices they make and the choices made by others in the market.

The assumption that competing companies depend on automatic substitution for market share may be simplistic. Only a minority of states require substitution; most instead have permissive laws. In these states, if a generic product is therapeutically equivalent to the prescribed product and the payer requires its use, the permissive state pharmacy law makes it possible for a pharmacist to substitute, in accordance with the patient's insurance, without consulting the physician. In these cases, the patient's insurance drives the product selection. State law just makes it possible to comply with the insurance without contacting the doctor. If a payer perceives the innovator's new product as less cost effective than available generic drugs containing the same active ingredient, it may decline to cover the product. A rational payer will adopt strategies that steer doctors and patients to less expensive products that are equally or adequately effective—not only those that are therapeutically equivalent, but also those that are not. In these cases, even if a doctor specifies a branded product, the patient's insurance might prompt a conversation among the doctor, pharmacist, and patient, ultimately leading to

modification of the prescription and dispensing of the cheaper copy of the innovator's first-version product.

In short, when an innovator introduces a new product into the market, generic companies will be able to introduce copies of the innovator's first product and they may or may not enjoy sales depending on the choices they make and the choices made by others in the market. In this scenario, products compete for the business of rational payers based on their comparative benefits and cost. Substitution may play almost no true role, and whether the innovator still markets its older branded product may be irrelevant.

HONEST CONVERSATION ABOUT REGULATORY REFORM

Many who argue for new regulation to address supposed evergreening perpetuate these three myths in their writing. Once these myths are laid bare, it becomes clear that the ultimate claim behind the metaphor—that *something* has been *extended* when an innovator introduces a newer product based on its continuing innovation with a particular active ingredient—cannot stand.

Careful review of the examples offered by proponents of reform yields a key insight about what they really want to address. In these situations (1) an innovator markets a drug product that would not exist *but for* a separate discovery earlier in time, typically a novel active ingredient, and (2) because it lacks generic competition, this newer product can be sold at supra-competitive prices, even though the patent on the active ingredient has expired.

On the one hand, there is nothing to dispute here. Empirical work supports the factual claim. Innovators introduce new products that result from continuing innovation over time, building on and incorporating earlier discoveries. The new products are generally protected by patents and exclusivity that expire later than the original protections on its active ingredient.

On the other hand, to suggest this is an "extension" is puzzling. There is no basis in current law to state a usual or expected length of time during which a company should be permitted to market related products at supra-competitive prices. Patent law does not provide a basis. It provides a fixed term for discrete inventions claimed. That term is not meant to cover *other* inventions that would not exist absent earlier inventions. And there is no basis in patent law to deny protection for a discrete invention that meets the patenting standards simply because the inventor has already enjoyed a patent term on another invention. Nor does FDA law provide a basis for stating a usual or expected length of time.

To say that this is wrong—that government intervention is warranted because of this "extension"—is a normative claim. Restated, the normative claim 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. This is a radical claim.

Some proponents of reform hint at the normative argument, talking about the "rightful" term of a patent, or the notion that the public "agreed to pay" for innovation with a 20-year patent term, or that after 20 years a "product" belongs in the "public domain." All of these things may be true, but they do not defend the normative claim described above. Those arguing for reform need to own the claim: that innovators should not enjoy supra-competitive prices for products that can be traced to one initial discovery after expiry of the patent associated with that initial discovery. If this rule is to be limited to medicines, rather than extended to all fields of innovation (including, for example, software), the exceptionalism must be justified. In short, if the underlying intuition behind the proposed regulatory reforms is that, after a fixed period, drug innovators should simply move on—that they should not enjoy revenue on new products that can be traced back in some fashion to the same new chemical entity—that has to be defended. To date, it has not been.

Policymakers cannot make reasoned and well-informed decisions about law and policy in this area if normative claims are not clearly stated and justified. They will need to consider the many subsequent medical products traceable to a single initial innovation, the differing ways subsequent medical products may provide important benefits (clinical or otherwise) to patients, and whether and how medical product innovation would proceed without the incentives for continuing innovation that have been available historically. Policymakers must also consider the roles that payers, physicians, and patients play—and should play—in the marketplace for medical products. All of these issues deserve careful attention before policymakers move forward with proposals for aggressive government intervention in the marketplace.

This is why the failure of reform proponents to grapple with the nuanced legal and factual context in which innovators and their competitors operate is so pernicious. Serious policy proposals should be based on rigorous evidence-based work that is careful and precise about the law and the facts. We would be better served if everyone acknowledged forthrightly that competitors may use abbreviated application pathways for comparatively inexpensive products containing the same active ingredient and may promote and sell those products in the marketplace to willing purchasers, subject to the same rules of truthful and non-misleading promotion as other sellers. Only by admitting these points can we discuss the real argument being made.

In the end, use of the "evergreening" term is problematic. It is a sloppy metaphor that conceals not only descriptive failures but also a failure to own and defend a radical—and important—normative claim. Serious writers about this topic should avoid the shorthand and focus on what matters: an actual description of the law and facts in play and the real normative claim being made. The term's meaninglessness makes it impossible for audiences to distinguish among situations that may be different, as a legal, theoretical, or normative matter, and that may call for differing policy solutions. Using the metaphor does a disservice to policymakers and the public. *R*