The United States Patient Protection and Affordable Care Act of 2010: Clarifying "Exclusivity", "Evergreening" and "Related Entities" Terminology

The United States Patient Protection and Affordable Care Act (PPACA) was signed into law on March 23, 2010. It establishes, among other things, a preliminary Food and Drug Administration (FDA) approval pathway for follow-on versions of innovative protein drugs. Such drugs, if approved, are products shown to be biologically equivalent to a licensed reference biological product (e.g., an FDA approved drug already on the market) and are commonly referred to as biogenerics, follow-on biologics or biosimilars.[1, 2] Title VII of the PPACA is similar in purpose to the Drug Price Competition and Patent Term Restoration Act of 1984 (i.e., the Hatch-Waxman Act [3]) in that both seek to improve public access to less expensive bioequivalent pharmaceuticals while maintaining the financial incentive for innovator companies to discover, develop and market new drugs. A major financial incentive for innovator biologics companies under the PPACA is a twelve-year period of data exclusivity for drugs approved via a Biologics License Application (BLA).[4, 5] This twelve-year period is analogous to the five-year exclusivity period under the Hatch-Waxman Act. During this potentially lucrative twelve-year exclusivity period, no follow-on biologic application, whether biosimilar or interchangeable with the innovator's reference drug, may be approved by the FDA.[6]

The Meaning of "Evergreening"

"Evergreening" of legal rights has a long history prior to follow-on biologic drug regulation, particularly in contract and patent law. Generally speaking, evergreening is an effective legal tactic whereby one entity (or related entities) effectively extends exclusivity rights by circumventing the spirit of the law, rather the letter of the law. For example, patent evergreening can occur when a patent holder

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[1] Use of the term "biogeneric" has fallen out of favor in discussions regarding follow-on biological drugs as it may imply an inaccurate comparison to generic small molecule drugs which are freely substitutable.

[2] For clarity, the term "follow-on biologic" will refer to the broader class of drugs that include both "biosimilar" and "interchangeable" biologics. The term "biosimilar" is reserved for the subclass of follow-on biologics that are merely similar to the reference biologic and require a prescription from a health care provider. The term "interchangeable" is reserved for the subclass of follow-on biologic that is essentially identical to the reference biologic and may be freely substituted without the intervention of a physician.

[3] *See* 21 U.S.C. §355(j).

[4] The 12-year "data exclusivity" period is calculated from the BLA approval date and is enforced only against *approval* of subsequent follow-on biologic applicants who have statutorily relied upon the clinical safety and efficacy data contained in the innovator's reference biologic drug application. Notably, FDA will not *accept* follow-on biologic applications for 4 years after the reference drug BLA was approved. This latter 4-year exclusivity period is referred to as "market exclusivity."

[5] *See* 21 C.F.R. 601.2 for the general provisions, including clinical trial requirements, for filing a BLA application with FDA.

[6] Importantly, the 12-year data exclusivity period does not prevent drug sponsors from alternatively submitting a BLA for follow-on versions of already approved biologics. *See* Teva Pharmaceutical's November 30, 2009 BLA filing for XM02—a follow-on version of Amgen's Neupogen™ (filgrastim).

amasses multiple patents on distinct attributes of a single drug product.[7] While the initial patent may protect the innovative biochemical compound, subsequent patents may be used to protect, for example: (i) clinical uses of the drug, (ii) methods of treatment, (iii) packaging, (iv) delivery profiles, (v) dosing regimens, (vi) routes of administration, (vii) drug combinations or (viii) drug polymorphs. Such a practice, while entirely legal, may persuade follow-on product manufacturers to wait for the last patent to expire before entering the market to eliminate the possibility of patent infringement and/or litigation. In this sense, long after the first chemical compound patent has expired, any additional "evergreened" patent exclusivity period(s) can potentially delay innovation and generic market entry.[8] However, under no circumstance is the length of any individual patent exclusivity period lengthened beyond its initial termination date.[9]

Similar misleading anti-competitive arguments exist in the drug regulatory field. Here, the exclusivity period granting agency is the United States Food and Drug Administration (FDA) not the United States Patent and Trademark Office (USPTO). The allegation is that the same BLA "sponsor or . . . other related entity" will accumulate multiple twelve-year exclusivity periods for subsequently approved BLAs for biologics having only minor modification(s) "to the structure . . . that does not result in a change in safety, purity or potency."[10, 11] Put another way, because innovator companies (and/or their "related entities") are free to file as many BLAs as they wish, the concern is that innovator drug sponsors will see this as an opportunity to obtain overlapping exclusivity periods for non-innovative, follow-on versions of their own drugs, culminating in decreased innovation and delayed market entry of affordable follow-on biologics.[12] However, as is the case for evergreening patent rights, the rationale behind such fears is largely misguided.

"Deciduous" Exclusivity for Innovators

Similar to the finite period of patent exclusivity, a rightfully obtained twelve-year data exclusivity period cannot be extended or "evergreened" into a thirteen-year (or longer) period by a subsequent BLA.[13] In keeping with horticultural parlance, BLA exclusivity rights are "deciduous" – the leaves of exclusivity die after a twelve-year maturity period allowing follow-on versions of biologic drugs referencing the now-expired BLA to enter the market.[14] Furthermore, as very few, if any, follow-on biologics will be identical counterparts to their reference drug, some of these follow-on versions will unintentionally turn out to be improved versions of the reference drug—a "biobetter"—and demand a market premium over their innovator counterparts.[15]

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[7] Importantly, each patent bears rightfully gained exclusivity periods granted by the United States Patent and Trademark Office (USPTO) according to Article I, Section 8, Clause 8 of the U.S. Constitution.
[8] This corporate patent strategy is offset financially by the possibility of patent claim invalidation, patent unenforceability or design-around strategies.
[9] To do so would constitute unlawful patent misuse. *See* 35 U.S.C. §271(d).
[10] *See* 42 U.S.C. §262(k)(7)(C)(ii).
[11] "Potency" is equivalent to efficacy. *See* 21 C.F.R.§600.3(s).
[12] Conservative pre-approval cost estimates per biologic are hundreds of millions to billions of U.S. dollars over a 10-year period.
[13] It should be emphasized that not all BLAs are approved. Failure of a BLA to get FDA approval is often financially ruinous to innovator companies.
[14] Similar to a finding of patent invalidation/unenforceability, FDA approved drugs may be taken off the market for safety concerns well before expiration of the 12-year exclusivity period.
[15] In such a scenario, the follow-on applicant will benefit enormously at the expense of the innovator by supplanting the reference biologic without conducting extensive BLA clinical trials. It is currently unclear if FDA will formally acknowledge "biobetter" status of follow-on biologics approved under an abbreviated BLA pathway.

The pejorative origin of the "evergreening" term in the follow-on biologics debate seems to derive from natural market forces in the medical community. This includes physician and patient reluctance to switch from an innovator drug to a follow-on version.[16] Additionally, biologics are currently not reimbursed in a manner that will incentivize the use of lower-priced follow-on biologics.[17] Finally, the lack of automatic substitution for most, if not all, follow-on biologics will also slow market entry. Companies developing follow-on biologics may be best served by increasing public awareness of these issues rather than demonizing the accumulation of exclusivity periods for biologically distinct drugs that have survived: (i) the risky and expensive clinical trial gauntlet, (ii) the subsequent FDA review process (including Advisory Committee decisions), and (iii) any post-market surveillance requirements.

Tightening the Two Loopholes

Closely related to the perceived evergreening issue, there are at least two other poorly defined concepts, or loopholes, in Section 262(k)(7) of the PPACA which describe who is ineligible for multiple twelve-year exclusionary periods.[18] These are (i) the "related entity" loophole and (ii) the "structural modification" loophole.

The structural modification loophole can be eliminated by alternate statutory language. The related entity loophole can be tightened by a more precise definition of what a related entity should be in light of statutory intent. This article will not comment further on the structural modification loophole other than to say that: (i) for patient safety concerns, a conservative approach should be taken that assumes any structural change in a biologic drug will result in a change in safety, purity and/or potency[19], and (ii) any statutory language seeking to regulate the eligibility of subsequent twelve-year exclusivity periods based on protein structure is fatally flawed.[20]

The statutory intent of Section 262(k)(7)(C) of the PPACA is to prevent anti-competitive behavior by denying a singular BLA sponsor, or their "related entit(ies)", any additional twelve-year data exclusivity period(s) for non-innovative versions of their own biologics. Indeed, the PPACA explicitly disallows exclusivity for supplemental BLAs.[21] The following exemplary alternate statutory language for Section 262(k)(7)(C) would strengthen the anti-evergreening intent of the PPACA and still foster innovation:[22, 23]

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[16] Innovator drug companies often develop strong sales and marketing contacts with physician and patients who are concerned about switching to follow-on drugs. This is particularly true for biologics with their unpredictable safety, efficacy and immunogenicity profiles.

[17] Biologic drugs are often delivered in a clinical setting as part of medical treatments, and are reimbursed by health insurers as part of patients' medical benefits rather than pharmacy benefits.

[18] Again, FDA only awards 12 years of data exclusivity to approved BLAs containing extensive and expensive pre-clinical and clinical trial safety and efficacy data owned by the sponsor.

[19] We are aware that this will necessitate some form of a (possibly abbreviated) pre-approval clinical trial and/or a post-approval pharmacovigilance study.

[20] An often-cited and scientifically reasonable argument is that <u>any</u> "structural" change in a biologic drug will <u>always</u> result in a change in either safety or potency. We offer preliminary language that takes emphasis away from the structure of the drug and onto the structure of the corporate sponsorship of the drug.

[21] *See* 42 U.S.C. § 262(k)(7)(C)(i).

[22] Emboldened text is alternative language for 42 U.S.C. § 262(k)(7)(C) suggested by the authors. Note the absence of the problematic "structural" language. Significantly, the suggested language would not necessarily prohibit 12 years of data exclusivity for a follow-on biological deemed superior by FDA to the reference drug (e.g., a "biobetter"). "Biobetter" biologics are neither closely similar nor interchangeable to a reference biologic. Rather, "biobetters" simply demonstrate superior safety and/or efficacy profiles. In light of statutory intent, it seems

(C) FIRST LICENSURE. Subparagraphs (A) and (B) shall not apply to a license for or approval of:

(i) a supplement for the biological product that is the reference product; or

(ii) any subsequent application for a biosimilar or interchangeable product filed by: (I) the same sponsor, (II) a related entity, (III) the same manufacturer, (IV) the same licensor or (V) any predecessor in interest of the biological product that is the reference product.

Additionally, the following contract language more precisely defines what type of related entity is ineligible for twelve-year market exclusivity based on subsequently approved BLAs:[24] This contract language is widely used and accepted throughout the business industry.

A "related entity" is an entity which:

(1) directly or indirectly controls,

(2) is controlled by or

(3) is under common control with another entity.

An entity shall be regarded as in control of another entity if it:

(a) owns, directly or indirectly, more than 50% of the voting stock or other ownership interest of the other entity or

(b) possesses, directly or indirectly, the power to (i) direct the management and policies of the other entity or (ii) elect or appoint more than 50% of the members of the governing body of the other entity.

Follow-on Biologics Are (Technically) Innovative Biologics

Due to the unpredictable safety and efficacy profiles of all biologic drugs, follow-on biologic drugs could alternatively be submitted for FDA approval under the traditional BLA pathway. If approved, the product would have the opportunity to be judged a "biobetter" by the market. This strategy would also allow the biobetter product to benefit from the twelve-year exclusivity period. Ultimately, it is up to corporate sponsors to decide whether to pursue BLA approval for follow-on versions of their own drugs or the drugs of their competitors.[25]

Rewarding successful BLA applicants with twelve years of data exclusivity seems to be a reasonable trade-off for assuming the financial risk associated with discovering, developing, marketing and monitoring biologically distinct drugs. However, corporate sponsors who blindly seek exclusivity for scientifically unique, yet arguably non-innovative versions of existing drugs ultimately do so at their own long-term peril. After all, without innovative drugs, manufacturers pursuing follow-on drugs products would have nothing to copy.

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reasonable to assume that a "biobetter" sponsor would only be awarded 12 years of exclusivity if approved via the BLA pathway (and not as a follow-on application).

[23] Alternatively, the following language for 42 U.S.C. § 262(k)(7)(C)(ii) may be used: "(ii) any subsequent application for a ***biological product that fails to demonstrate an improvement in safety or efficacy*** filed by . . . ."

[24] All other non-enumerated entities would be eligible for additional twelve-year exclusivity periods.

[25] One strategy would include innovator drug sponsors establishing (and ultimately acquiring) "unrelated" corporate entities to manufacture "authorized follow-on biologics" of their own products to help facilitate market acceptance.

If you have any questions about this article, or would like to discuss this topic further, please feel free to contact:

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