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Approval Regs Must Change To Keep Up With Biologics Tech

By **Eva Temkin and Jessica Greenbaum** (September 15, 2023, 4:45 PM EDT)


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The U.S. Food and Drug Administration operates under two different statutory frameworks in its review and approval of drugs: Section 505 of the Federal Food, Drug and Cosmetic Act governs drugs that do not fit within the definition of "biological product," while Section 351 of the Public Health Service Act governs biologics.

These frameworks have much in common. They have a similar user fee program. They share general requirements related to evidence supporting approval, with the FDA equating the drug standard of safety and substantial evidence of efficacy with the biologics standard of safety, purity and potency. The same teams of people even review applications in the FDA's Center for Drug Evaluation and Research.

The similarity in these paradigms has particularly been the case since Congress directed the FDA in 1997 to "take measures to minimize differences in the review and approval of" new drug applications, or NDAs, and biologics license applications, or BLAs.[1]

Yet there are also differences: different implementing regulations — including different post-market change and inspection-related requirements — and even differences in how the FDA handles transfers of approved applications. Perhaps the most significant difference as a legal matter is the variety of approval pathways.

The modern framework for new drug approvals includes three pathways:

- Stand-alone applications supported entirely by an applicant's own data, or by data to which they have a right of reference, such as the 505(b)(1) pathway;[2]
- Generic drugs, which duplicate reference listed drugs and rely on the FDA's safety and effectiveness findings with respect to those drugs;[3] and
- The middle ground of the 505(b)(2) pathway.

NDAs submitted under the 505(b)(2) pathway rely, in part, on the FDA's finding of another drug as safe and effective,[4] but they can also innovate by leveraging preexisting information, including that in published literature, to support changes and improvements.

For biologics, there are only two pathways:

- A stand-alone BLA licensed under section 351(a) of the PHSA; or
- A biosimilar BLA licensed under section 351(k).

All new biologics are submitted in stand-alone BLAs, which are required to contain all the data and information necessary to meet the approval standard. There is no pathway for biologics to build upon work already done to, for example, bring second-generation platform technologies to patients or to streamline development of a novel combination of a new biologic with a previously approved drug.

Historical Approach to Leveraging Data in BLAs

Historically, the FDA has not permitted BLAs to leverage findings of safety, purity and potency — which encompasses safety and effectiveness — from outside the application, not even from published literature. This rule is a matter of policy; there are no outright limitations in the PHSA on what types of data and information can or cannot be included in a stand-alone BLA.

The rule originated in an era when data reliance was simply impermissible as a scientific matter. Antibody drug conjugates had not yet been invented, and cell and gene therapies were in the distant future, if imaginable at all. The precise manufacturing process was critical to BLA approval, so each BLA needed to contain complete information to demonstrate the safety, purity and potency of that process.

More recently, science has evolved to the point where this binary system is squeezing out some types of innovation for biologics that, for drugs, have been accomplished through the 505(b)(2) pathway. For example, much attention recently has been paid to the use of platform technologies — technologies that can be incorporated or used in more than one drug or biological product — to streamline the development of cell and gene therapies, like multiple gene therapies that target different defects using the same vector.

Dr. Peter Marks, director of the FDA Center for Biologics Evaluation and Research, has said that he would like to see these types of gene therapy platform technologies functioning in the way of modern soda dispensers, "very much like one of these Coke dispensers that can make 100 or 1,000 different Cokes"[5] — the primary process is approved, and product-specific changes can be made at the push of a button.

The promise of these types of technologies can only be fulfilled, however, if the regulatory paradigm keeps pace with the scientific cutting edge. Yet very little attention has been paid to the entrenched legal and policy restrictions that might stop a BLA from leveraging earlier platform technology or published data and information.

The December 2022 signing of the Food and Drug Omnibus Reform Act, or FDORA, created a designation program aimed at expediting development of platform technologies and permitting single supplemental application for multiple changes. That designation may prove very useful, but it is limited to circumstances in which the applicant is relying on its own data — or with a right of reference — and the platform technology is identical to that previously approved.[6]

FDORA does not address the possibility of relying on existing data in a broader context, such as for new combinations or second-generation platforms. Those types of biologics applications are left in the regulatory gap described above, meaning BLAs must redemonstrate safety, purity and potency from scratch, resulting in slower, more expensive development programs.

A Legal Structure for the Future

Over the past year, the FDA has begun to consider this problem and how it might be solved. CBER's Marks explained in October 2022 that the FDA could start

> allowing an individual company to leverage the information from one application to another, and then, if that's working well, [the FDA] can consider expanding that concept further.[7]

CDER has also made small inroads, recognizing in May 2023 guidance an exception, albeit a very narrow one, under which a stand-alone BLA may rely on "generally accepted scientific knowledge."[8]

Yet, to ensure that these scientific improvements in manufacturing technologies translate into maximal patient benefits, additional regulatory reform is needed.

One option is new legislation. If a stand-alone BLA is "too hot," and the biosimilar pathway "too cold," new legislation could create a "just right" middle pathway for biologics developers seeking to harness prior work, draw on published literature, and more, further innovate without unnecessary cost and delay.

While awaiting an appropriate vehicle for such legislation, the FDA could enhance flexibility in BLAs through rulemaking, or potentially even guidance. The agency can revisit its ban on leveraging information in BLAs, which science has rendered obsolete.

The law needs to develop to avoid creating drag on the rapid scientific progress in this area. Otherwise, applicants may not be able to take full advantage of the promise of platform technologies. Innovators seeking to build on their earlier work, and those looking to create bespoke therapeutics that require process changes for every patient — or every group of patients — will have development programs delayed or even derailed.

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[1] Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115, 105th Cong., § 123(f) (1997).

[2] 21 U.S.C. § 355(b)(1).

[3] Id. § 355(j)(5); see also FDA Guidance for Industry, Determining Whether to Submit an ANDA or a 505(b)(2) Application (May 2019).

[4] 21 U.S.C. § 355(b)(2).

[5] Derrick Gingery, Could US FDA Move Gene Therapy Regulation To Device Center In Years To Come?, Pink Sheet (Nov. 25, 2022), available at https://pink.pharmaintelligence.informa.com/PS147228/Could-US-FDA-Move-Gene-Therapy-Regulation-To-Device-Center-In-Years-To-Come.

[6] 21 U.S.C. § 356k(f).

[7] https://www.genengnews.com/gen-edge/peter-marks-outlines-fdas-commitment-to-advancing-gene-therapies/.

[8] See FDA Draft Guidance for Industry, Generally Accepted Scientific Knowledge in Applications for Drugs and Biological Products: Nonclinical Information (May 2023).