TO BLA OR NOT TO BLA?

An approval pathway for biosimilars has existed in the US for nearly 2 years, but the practical implications of this new option are still difficult to ascertain. Although analogy to the generic pathway for small molecule drugs is attractive, unique characteristics of biologics defy such straightforward logic. Further FDA guidance on several points is needed to accurately assess the risks and benefits of the different approval pathways for biologics.

Following in Europe's footsteps, the US now has an alternative approval pathway for biologic therapies, intended to reduce some of the hurdles associated with a full Biologics License Application (BLA). Small molecule drugs have had an alternative approval pathway for years, ever since the passage of the *Hatch-Waxman Act* in 1984. Now, for the first time, companies can choose between two regulatory approval pathways for marketing biologics in the US.

For small molecules governed by Hatch-Waxman, the choice is clear: The first company to get a new drug approved must conduct extensive testing for safety and efficacy of the drug, but in return receives a set of protections against competitors who also want to market that drug. A competitor must await the end of these protections, but then can largely rely on the originator's safety and efficacy data, avoiding much of the expense the originator incurred in gaining approval for its product. It is a system that is widely viewed as fairly respecting the needs of innovator companies whilst fostering the introduction of safe and inexpensive generic medications. In part, the system works because small molecule drugs can be reliably purified and characterized, making it easy to compare the content of a generic product to the originator's approved drug product and predict its effects on patients. For biologic agents, this premise simply fails.

Biologics are comparatively enormous and intractable molecules and are made not by carefully controlled chemical reactions, but by living cells. Techniques that are routinely used to understand the structure and purity of small molecule drugs are confounded by the size and complexity of biologics. A chemical reactor can be trusted to churn out the same molecule from the same reagents time and time again. Not so a cell, whose delicate machinery can be affected by minor variations in temperature, pH and other environmental conditions. In fact, biologics are rarely, if ever, limited to a single defined entity; typically, biologics contain a range of discrete molecular entities, differing in post-translational modifications or other minor structural features. Unfortunately, minor structural features can have significant effects on the way a biologic interacts with a patient's body. In short, nothing about biologics will ever be as simple as small molecule drugs.

So the process for approving biosimilars simply can't be as straightforward as the Hatch-Waxman regime. In the wake of *Biologics Price Competition and Innovation Act* of 2009 (BPCIA), FDA faces the unenviable challenge of deciding how much testing of a biosimilar is necessary to be confident that it is as safe, pure and potent as the originator biologic. This decision is key to the success of biosimilars in the US. Too much testing, and the cost of biosimilar clinical trials threatens the fundamental economic incentive of the biosimilar pathway. Too little testing, and high-profile adverse events could forever ruin the market for biosimilar products. And not all biologics are alike. Peptide therapeutics, antibodies, gene therapies and stem cells each have their own idiosyncracies and potential risks; a one-size-fits-all approach is unlikely and unwarranted. Indeed, FDA has already signalled that biosimilar applications will be evaluated individually on a fact-specific, case-by-case basis, looking to the totality of the evidence. So far, there is little clarity as to exactly how much testing FDA will require of those who pursue the biosimilar pathway.

Legal Pathways

The legal barriers a biosimilar applicant faces are, however, more clear. A biosimilar application can't be filed for 4 years after the referenced originator biologic is approved, and the biosimilar product can't be approved for 12 years after that approval. The follow-on applicant who chooses the traditional BLA pathway instead can file — and be approved — at any time, lengthening the product's market lifetime. If an approved product attracts multiple biosimilar follow-ons, the lure of the traditional BLA pathway increases, because the expiry of the originator's 12-year market exclusivity could open the floodgates to an onslaught of "me-too" biosimilars. A follow-on manufacturer that opts for the traditional BLA pathway can beat these biosimilars

to the market, command a higher price point, achieve greater market share and gain a brand recognition and differentiation edge compared with biosimilars.

The follow-on manufacturer who obtains regular BLA approval receives the same 4- and 12-year protections against biosimilar applicants as the originator. This protection, however, may not be particularly meaningful if competitive products can enter as biosimilars of the originator product at the earlier expiry of its exclusivities. Conversely, a regular BLA applicant — but not a biosimilar applicant — can put forward a product that meaningfully differs from an approved biologic in terms of structure, safety or efficacy. An improved product can obviously outcompete an originator product — and its biosimilars — on therapeutic merits.

Patent Protection

Another complicating factor is patent protection for the originator product. The patent landscape will differ for each product and will remain relevant whether an applicant chooses a traditional BLA or the biosimilar pathway. Unlike the world of generic small molecules, where patent litigation can trigger an automatic 30-month stay of the generic's approval, patents have no role in the biosimilar approval process. Still, patents can present a barrier to biosimilar market entry. In some cases, the long market exclusivity for biologics may mean that biosimilar applicants face few or no patents after approval; but strong patents in effect during that 12-year period may diminish the incentives for early approval via a traditional BLA.

Occasionally, the originator's life-cycle management strategies may provide patent protection that outlasts the 12-year statutory market exclusivity. The resulting patent disputes regarding biosimilars will be governed by the byzantine system of rules established by the BPCIA. In some circumstances, an applicant might seek to force the innovator down this dark alley; otherwise, choosing the regular BLA route completely bypasses this complex and arcane system in favour of ordinary patent litigation. Overall though, the BPCIA does little to substantively affect the role of patents in the biologics marketplace, so would-be biosimilar applicants can assess the patent landscape protecting their target products of choice and understand the role of patents in their approval and marketing strategies regardless of their route of approval.

Nomenclature

One more murky area of biosimilar regulation is nomenclature. Will biosimilar products have the same generic name as the originator product? If not, will the names be similar? Will products approved through a regular BLA have more dissimilar names, even if the products are similar enough to an existing product to use the biosimilar pathway? Follow-on manufacturers that intend to devote few resources to sales and marketing may desire names that benefit from association with the name of the originator product; those that plan to invest in aggressive sales and marketing efforts may want the market differentiation that comes from having a dissimilar name.

Conclusion

For now, only further guidance from FDA — either in the form of regulations or guidelines, or in the treatment of early biosimilar applicants — can allow companies to meaningfully project the potential savings of the biosimilar pathway or the value of a traditional BLA. Until then, the biotech world watches — anxiously — and waits. **Pharma**

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