Biosimilars: economics and intellectual property

Innovators face new challenges and opportunities relating to their IP rights with the onset of biosimilars, say industry experts

The provision of health insurance and new insurance delivery structures have garnered significant attention for the Affordable Care Act, but another aspect of that law has focused attention on intellectual property considerations within the life sciences industry in the US.

The Biologics Price Competition and Innovation Act (BPCIA) created regulatory pathways for biosimilars (copies of branded biologic products).

While biosimilars are already available in Europe, as of August 2014 only two biosimilars have been accepted for review by the US Food & Drug Administration (FDA) under the auspices of the BPCIA: the Sandoz version of Amgen's Neupogen and Celltrion's version of Johnson & Johnson's (J&J's) Remicade.

With regulatory approval pathways encouraging more competition among manufacturers of biologics, there follows the prospect of increased litigation and other threats to IP. We summarise some of the initial concerns for innovators facing the prospect of biosimilar approval and commercialisation. While we focus on IP issues, we also note that the onset of biosimilars may have implications for litigation involving product labelling, antitrust, and product liability.

The differences between biosimilars and more conventional generic small molecules are likely to alter the context for IP disputes in several ways. For instance, biosimilars may be subject to higher development costs, may involve more complex production or administration (with accompanying patents and trade secrets), and may be more capital intensive to manufacture and distribute. These potential characteristics contribute to a competitive environment between the reference product and the biosimilar that is very different from what we would expect based on experience with small-molecule generics.

In turn, these differences may affect innovators' considerations for protecting IP. For example:

- Indication extrapolation: the experience of innovator biologics shows that the same biologic therapy might demonstrate safety and efficacy across a range of fairly disparate indications, such as Remicade's indications for rheumatoid arthritis, Crohn's disease, and psoriasis. Would all of an innovative reference product's indications be shared with a biosimilar or would managed care organisations (MCOs) encourage substitution of a biosimilar for all indications of the referenced innovator product? How will the potential for indication extrapolation regarding the molecule compare with method-of-use patents that are more indication-specific?
- 'At-risk' launches: there is currently no 'Orange Book' for biologics. Accordingly, biosimilars considering US launches before the conclusion of patent litigation (similar to small-molecule 'at risk' generic launches) may face a more burdensome process to identify the relevant IP protecting the reference biologic. Nonetheless, the potential damages exposure for biosimilars launching at risk may be less than for small-molecule generics as penetration rates and price differentials are likely to be lower, particularly if the biosimilar approval does not allow for interchangeability with the reference product. There may also be a greater opportunity for the innovator to obtain a preliminary injunction founded on irreparable harm, due to the expected discontinuation of ongoing research and development efforts into other disparate indications if the biosimilar were allowed to enter.
- Patent thickets and competition challenges: Biologics are complex molecules with the potential for a greater number of patents over the compound, methods of use, and manufacturing processes, not to mention possible trade secrets concerning the manufacturing process. A broad IP portfolio, however, may also raise competition concerns if it is deemed to inappropriately stifle follow-on innovation.
- Allocation: recent judicial decisions have examined the use of the 'entire market value rule' to determine the appropriate

royalty base for alleged infringement of IP. With a broad IP portfolio covering a biologic, however, it may be challenging to determine the appropriate level of damages attributable to infringement of a subset of the patents in the portfolio. Damages analysis may also be complicated by a scarcity of comparable market transactions involving biologics and similar technologies.

Damages assessment

The arrival of biosimilar applications provides an impetus for innovator companies to consider the evolution of their patent litigation strategies. Litigating small molecule patent challenges often involves discussion of 'non-infringing alternatives'. With more IP involved, biosimilar manufacturers may find it more difficult to identify viable non-infringing alternatives.

As a result, there may be an increased need to develop methods that can disentangle the sources of demand for the biologic product and apportion value appropriately. While market research methods in this area are promising, the complexity of biologic agents might challenge the ability of market research targets (MCO representatives, physicians, or patients) to provide accurate information for valuation assessments.

It may be tempting to rely on the past experience of generic small-molecule drugs to predict how the introduction of biosimilars may affect sales of the innovator product and other therapies that might be used for similar indications. This, however, is likely to be a dangerous assumption. Due to the large price-cost margin that tends to exist in the pharmaceutical industry, small-molecule generics may be able to offer significant price discounts to the innovator product. Accordingly, payers may capitalise on the potential for savings by requiring generic substitution among interchangeable products.

With respect to biosimilars, however:

- The regulatory authority may not designate the products as 'interchangeable' and physicians and patients may be less accepting of the biosimilars than they are of small-molecule generics;
- The more complex manufacturing processes are likely to restrict the number of potential biosimilar entrants for any particular product; and
- The consequent price-cost margin is unlikely to be able to support the price differentials that have been found for some generic products.

The result is likely to be lower biosimilar penetration rates and price erosion than one otherwise might expect, with consequent implications for damages assessment.

With the onset of biosimilars, innovators face new challenges and opportunities relating to their IP rights. Proper attention to the differences to the small-molecule case can help innovators to develop prudent responses to these challenges and opportunities. **IPPro**

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