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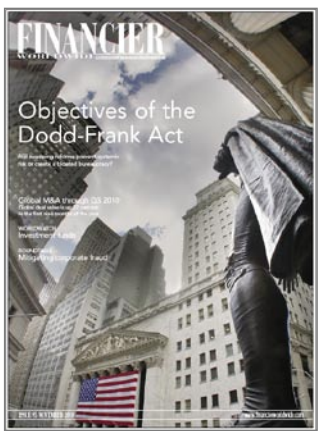

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INTELLECTUAL PROPERTY LITIGATION

Recent legislation impacts development of biologics

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Recent biologics legislation in response to the increasing prevalence of biologic products on the market highlights the importance of such products and has changed the legal and regulatory landscape with respect to biologic products. With these changes arise numerous considerations for biologics businesses and investors alike. Those considerations can affect a company's decision, among other things, to pursue development of novel biologic products as opposed to biosimilar products.

Biologic exclusivity

One of the most important effects of the new legislation pertains to exclusivities associated with types of biologic products. Under the new legislation, there are three categories of biologics: novel biologics, biosimilar products and interchangeable biosimilar products. Interchangeable biosimilar products can be switched with the reference product without the prescriber's consent at a pharmacy, while biosimilars without interchangeable status cannot be switched absent prescriber's consent. A novel biologic can receive 12 years of marketing exclusivity upon Food and Drug Administration (FDA) approval of its biologic licence application (BLA). 42 U.S.C. § 262(k)(7)(A). An applicant for a biosimilar product ('subsection (k) applicant') to a reference product sponsor (RPS, a novel biologic with an approved BLA) that is first to achieve an 'interchangeable' status from the FDA, will receive a maximum of one year of biosimilar marketing exclusivity. See 42 U.S.C. § 262(k)(6). All other biosimilars do not receive marketing exclusivity. *Id*. Thus, in order to obtain biosimilar exclusivity, those involved in biosimilar development will be driven to receive the first determination of interchangeability, which is not necessarily dependent on who files a subsection (k) application with the FDA first.

Current standards for biosimilar approval

In order for a novel biologic to obtain BLA approval, extensive analytical and clinical trial data must be presented to the FDA. Though it might be assumed that less testing is required for biosimilar approval similar to what is required for generic small molecule products, the recent legislation is not clear regarding what type of testing will be required. *See* Thomas Gyrta, 'Biosimilar Development Progresses, Without FDA Guidelines', Wall Street Journal (Aug. 16, 2010). A 'biosimilar' is statutorily defined as a biologic product that "is highly similar to the reference product" and has "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product". 42 U.S.C. § 262(i)(2). But the above language does not describe what degree of similarity is required to satisfy the 'highly similar' standard and how 'clinically meaningful' is defined. Statutory language regarding the testing required is similarly unclear.

Further, to show biosimilarity, "analytical studies demonstrating that the biological product is highly similar to the reference product not withstanding minor differences in clinically inactive compounds" are called for. § 262(k)(2)(A)(i)(I). What the FDA will consider 'minor differences' and what sort of analytical studies the FDA will require, among a multitude of options varying in time and cost expenditures, is currently unknown.

Also required to show biosimilarity are "a clinical study or studies… that are sufficient to demonstrate safety, purity and potency". 42 U.S.C. § 262(k)(2)(A)(i)(I). Again without further guidance or statutory provisions, it remains unclear what clinical studies will be required by the FDA. Adding further ambiguity to these provisions is that the FDA can waive any of the aforementioned biosimilar requirements in its discretion. 42 U.S.C. § 262(k)(2)(A)(ii). In what scenarios such requirements will be waived is uncertain.

To show interchangeability, a biological product must be biosimilar to the reference product and must be expected "to produce the same clinical result as the reference product in any given patient". 42 U.S.C. § 262(k)(4)(A)-(B). Many other questions arise here. What clinical testing is expected? What degree of similarity must be shown between clinical results? How many patients must be studied? Can any requirements be met by in vitro testing? Moreover, for those products "given more than once to an individual" another interchangeability requirement is that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the ref-

erence product is not greater than the risk of using the reference product without such alternation or switch". 42 U.S.C. § 262(k)(4)(A)-(B). But again, there is no guidance as to what type of analytical or clinical data will meet this requirement.

Uncertain costs

An important part of any pharmaceutical development project is being able to properly predict what resources will be required to complete the regulatory approval process. Without knowing exactly what analytical and clinical studies (which can be extremely resource intensive) must be performed to obtain regulatory approval, such figures are near impossible to calculate. Based on the current uncertainty of the FDA's analytical and clinical study requirements to prove biosimilarity, it is possible that costs for developing a biosimilar could rival those of novel biologic development. Additionally, if a biosimilar does not achieve interchangeability, a substantial advertising cost may be incurred to educate prescribers about the biosimilar, since it cannot be switched at a pharmacy absent prescriber consent. Thus, companies interested in biologics development may choose to develop novel biologics rather than biosimilars, since a comparable time and cost investment could result in 12 years of exclusivity rather than one year of biosimilar exclusivity.

Forfeiture of exclusivity

Potential forfeiture of exclusivity must be a consideration taken into account by a company before deciding whether to develop a novel biologic or biosimilar. Inter alia a subsection (k) applicant who is the first to be determined interchangeable can lose part, if not all, of its exclusivity where it has been sued for patent infringement, wins, yet fails to begin marketing within six months after a final court decision has been rendered on all patents. 42 U.S.C. § 262(k)(6). Since a subsection (k) application can be filed any time after four years from the reference product's BLA approval ('Year 4') and cannot be approved until 12 years from BLA approval, ('Year 12'), applicants should be aware that they can trigger forfeiture provisions by receiving a determination of interchangeability too quickly. For example, if a subsection (k) applicant files on Year 4, gets sued for patent infringement and obtains both an interchangeability determination and final court decision for the lawsuit three years before Year 12, forfeiture of exclusivity would occur. As can be seen, subsection (k) applicants are in a precarious situation of applying early enough to achieve the first interchangeability status, yet late enough to avoid forfeiture provisions. This significant uncertainty may also weigh in favour of developing novel biologics over biosimilars.

Conclusion

From a practical standpoint, due to the molecular complexity, difficulty of manufacture and risk of clinical trial failure for biologics, all companies involved in development of biologics – whether novel biologics or biosimilars – will require significant financial resources and sophisticated development/production facilities. Ultimately, the decision on, among other things, whether to develop novel biologics versus biosimilars will depend on a company's evaluation of the factors discussed above. Since costs of developing a biosimilar could approach the costs of developing a novel biologic and the risk of interchangeable exclusivity forfeiture exists for biosimilar applications, the path of developing novel biologics may be more fruitful than developing biosimilars under the current statutory landscape. ■

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