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INTELLECTUAL PROPERTY
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Purple Book Launches New Chapter in Generic Drugs

FDA creation will help reduce cost of biologically derived medication

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Biologics, namely biologically derived therapeutic agents such as viruses, vaccines, blood products and nonsynthetic proteins, account for a large and growing portion of total spending on prescription medicines in the U.S. Biologics include unique treatments for patients with previously untreatable cancers or devastating genetic disorders, such as Ketruda, for treatment of advanced melanoma, and Cerezyme, for the treatment of Gaucher disease.

While biologics account for only a small percentage of the total prescriptions written, they are very expensive. Biologics accounted for at least 18 percent of total prescription medicine costs in 2012, and costs for treatment with a single biologic medicine can exceed $100,000 per year. The amount spent on biologic medicines is expected to increase substantially. The reason for the high cost of biologics is in part because of the lack of generic equivalents. While regulations for the approval of conventional small-molecule drugs were covered by the 1984 Hatch-Waxman Act, these regulations did not apply to biologics. Until the passage of the Biologics Price Competition and Innovation Act in 2010 (the BPCIA), the legal framework for approval of generic biological drugs did not exist, and until quite recently the legal structures needed for approval of generic biologic drugs had not been implemented. The Food and Drug Administration's (FDA) recent creation of "The Purple Book" is an important step toward the approval of less expensive biosimilar or biointerchangeable biologics.

The FDA Purple Book borrows its name from the FDA Orange Book, a Hatch-Waxman Act-required publication, listing approved drugs, their patent exclusivity and recognized generic equivalents. The FDA Orange Book was thus named because it was originally printed on orange paper. When the FDA needed a familiar name for its new book listing licensed biologics with the formal title "Lists of Licensed Biological Products with Reference Product Exclusivity of Interchangeability," it chose to call it "The Purple Book."

It should be noted that under the Food, Drug, and Cosmetic Act, conventional drugs are "approved," whereas under the Public Health Service Act, biologics are "licensed." The Purple Book is actually two lists, the Center for Biologics Evaluation and Research List of Licensed Biological Products (the CBER List) and the Center for Drug Evaluation and Research List of Licensed Biological Products (the CDER List).

The FDA Purple Book includes the date a biologic product was licensed, whether the biologic product is a reference product and whether any biosimilar or biointerchangeable products for a listed reference product exist. The Purple Book does not list exclusivity expiration dates for biologic products and also does not list the patents covering the biological product. To date, no biosimilar or biointerchangeable biologics have been approved, though the FDA has accepted its first applications for biosimilar products.

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Comparable to Generics

The Purple Book will allow pharmacists, or more likely pharmacy benefits managers, considering substitutes for branded biologics to ascertain whether the FDA has licensed a less expensive "biosimilar" version that can be prescribed instead of a reference-listed biologic medicine with additional physician approval, or a "biointerchangeable" version that can be substituted by a pharmacist without intervention from the prescribing health care provider. Thus, the biointerchangeable version is most comparable to a generic conventional drug.

The greater significance to pharmaceutical patent attorneys is the Purple Book's listing of dates of initial FDA licensing for reference products, which allows a follow-on biologics manufacturer to determine when the product's market and data exclusivity will expire. Under the BPCIA, an application for a biosimilar or biointerchangeable biologic drug under §351(k) may not be submitted until four years after the first FDA licensing of the reference product, and

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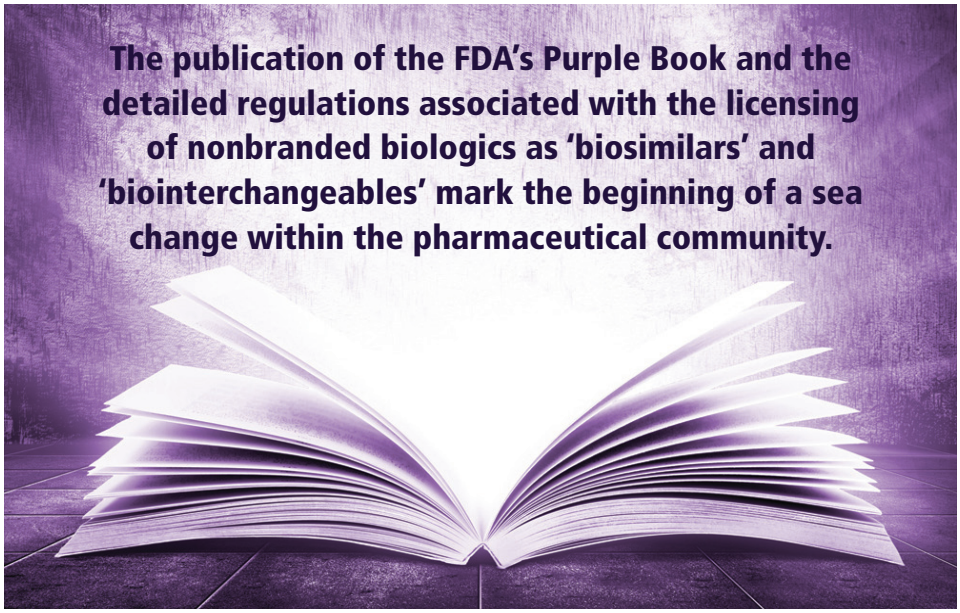
an application relying on the reference product's clinical trial data may not be approved until 12 years after first licensure of the reference product. This differs from the Hatch-Waxman Act, which has only a five-year data exclusivity period for conventional drugs, and can in some cases effectively extend the monopoly period for biologics beyond the life of the underlying patents. The Purple Book's listing of FDA licensing dates starts the clock for follow-on competition, and the industry expects the ready availability of information on biologic approvals will speed the development of biosimilar and biointerchangeable biologic medicines.

Much more is required under the BPCIA for FDA licensure of a biosimilar or biointerchangeable biologic product than is for FDA approval of a generic drug. The additional requirements are partly attributable to the differences between traditional drugs and biologic medicines. Once a drug has been discovered and its structure known, any competent pharmaceutical manufacturer can replicate the drug. Thus, the FDA approval process for generic drugs is quite straightforward. The generic manufacturer only has to show that the drug is chemically identical and that its formulation meets two criteria of bioavailability, Cmax and AUC24, when administered to patients. The generic manufacturer must also state that either there are no unexpired patents listed in the Orange Book for the drug, or that the listed patents are either not infringed or invalid.

Biologic medicines include larger and much more complex molecules than traditional drugs, and are typically produced by living cells. It is impossible to precisely replicate some biologic medicines without having access to the exact cell line the first manufacturer used. There can also be considerable differences in activity of otherwise identical biologic medicines produced by different methods. Unlike generic drug approval under the Hatch-Waxman Act, the BPCIA requires a certain amount of clinical testing to show biologic medicines made by a follow-on manufacturer are biosimilar or biointerchangeable. The FDA uses a totality of evidence approach to determine biosimilarity, and requires that there are no meaningful differences in safety, purity and potency. The BPCIA also requires a complex exchange of patent information between the reference product producer and the follow-on manufacturer .

Patent Phases

The patent information exchange has a disclosure phase, a contentions phase and a dispute resolution phase. The BPCIA information exchange process begins with the follow-on manufacturer informing the reference product manufacturer of the existence of the follow-on application within 20 days of the application's acceptance. The reference product manufacturer must then notify the follow-on application of all patents it owns that it believes claim the reference product, including patents to methods of manufacture of the product.



After seeing the reference product's list of patents, the follow-on manufacturer must, within 60 days, either state that it will not market its product until after the relevant patents have expired or it must state why the listed patents are not infringed by the follow-on biologic, and it may optionally provide a list of patents it believes could be asserted against its follow-on product. If the reference product manufacturer and follow-on manufacturer can agree on the patents that may be infringed, the parties proceed to litigation.

If the parties do not agree to the patents for an infringement suit, then the dispute resolution provision of the BPCIA is triggered to make this determination. This phase includes a procedure by which the parties exchange first the number of patents they expect may be infringed, and then the lists of potentially infringed patents, on a schedule set forth in the BPCIA . The reference product manufacturer then must commence the infringement action within 30 days of the conclusion of the dispute resolution phase.

In a recent case, Sandoz Inc., the generic pharmaceuticals division of Novartis AG, attempted to license a follow-on biologic but avoid the BPCIA process by seeking a declaratory judgment that its biosimilar version of Amgen Inc.'s Enbrel did not infringe certain patents. The court dismissed the action and held that no lawsuit could be filed unless and until the mandated exchanges of information had been completed. Thus, it appears that, at least so far, the courts intend to enforce the BPCIA procedures.

The publication of the FDA's Purple Book and the detailed regulations associated with the licensing of nonbranded biologics as "biosimilars" and "biointerchangeables" mark the beginning of a sea change within the pharmaceutical IP community. A path for generic biologics now exists and, thus, IP professionals need to prepare both patent prosecution and litigation strategies to accommodate the new landscape. Attorneys preparing patents for biological agents must do so in the shadow of potential litigation through the BPCIA procedure, and attorneys in IP litigation will need to understand and comply with the BPCIA procedure, and help their clients navigate the patent exchange process. In particular, the patents in the exchange must be chosen carefully, as once the patent lists are finalized they restrict the subsequent litigation.

Pharmaceutical companies are beginning to file applications under the BPCIA for licensed generic biosimilars. Sandoz's license application for its biosimilar version of Amgen's Neupogen is the first attempt at using the new rules to license a generic biologic; Celltrion's filing for a biosimilar version of Janssen Biotech Inc.'s Remicade is the second. As some of the biggest-selling biologics start to approach their own patent cliffs in the near future, the push for generic versions can be expected to intensify. With knowledge of and attention to the workings of The Purple Book and the BPCIA, pharmaceutical IP attorneys can help their clients meet the new challenges posed by generic biologics. ■