FDA INTENDS TO GRANT FIVE YEARS OF MARKET EXCLUSIVITY TO FIXED-DOSE COMBINATION DRUGS CONTAINING ONE NEW DRUG SUBSTANCE

Fixed-dose combination drug products are becoming increasingly important in the treatment of patients with diabetes, cardiovascular disease, and infectious disease. Within the last two decades, the U.S. Food and Drug Administration (FDA) approved 19 new drug applications (NDAs) for fixed-dose combination drugs containing at least one new drug substance. More than half of these NDAs were approved in the last seven years. As with the development of any pharmaceutical product, developers of fixed-dose combination drugs will seek to maximize the patent protection and market exclusivities provided by the United States Patent and Trademark Office (USPTO) and the FDA, respectively.

In the United States, the two main protections available to safeguard fixed-dose combination drugs are utility patents and market exclusivities.

Patent-Based Exclusivity

Utility patents are granted by the USPTO. The term of a utility patent begins at issue and is limited to 20 years from the filing date of the earliest non-provisional application upon which the patent is based. Utility patents can be extended for unreasonable USPTO delays in examining patent applications by patent term adjustment. For fixed-dose combination drugs, the term of a United States patent also may be extended for delays arising from the FDA approval process by patent term extension.

Market-Based “Data” Exclusivities

Fixed-dose combination drugs also are protected from competition by market exclusivities granted by the FDA (not the USPTO).

New drugs approved by the FDA, including fixed-dose combination drug products, are eligible for different terms of market exclusivity depending on the previous approval status of their active ingredient(s), whether the approval is for an orphan indication, and whether the drug has been studied in pediatric patients.

1 Janumet, a combination of the anti-diabetes medicine Glucophage (metformin HCI) and the dipeptidyl peptidase-4 (DPP-4) inhibitor Januvia (sitagliptin), is a combination drug targeting type II diabetes.
2 Caduet, a combination of the blood-pressure-lowering drug Norvasc (amlodipine besylate) and the cholesterol-lowering drug Lipitor (atorvastatin calcium), is a combination drug targeting cardiovascular disease.
3 Truvada, a combination of the nucleotide analog reverse transcriptase inhibitor Viread (tenofovir disoproxil fumarate) and the nucleoside reverse transcriptase inhibitor Emtriva (emtricitabine), is a combination drug targeting HIV infection.
5 id.
6 For U.S. utility applications filed on or after June 8, 1995, and excluding the effects of, e.g., terminal disclaimer(s), patent term adjustment, and patent term extension. See 35 U.S.C. § 154(c).
10 Market exclusivity prevents submission to the FDA and/or approval of any abbreviated new drug application (ANDA) or Federal Food, Drug, and Cosmetic Act (FD&C Act) § 505(b)(2) application that refers to the approved drug. It is worth noting that market exclusivity does not block submission, review, or approval of a FD&C Act § 505(b)(1) NDA. Also, a § 505(b)(2) application or ANDA may be submitted after the expiration of four years from the date of NDA approval, for drugs having five years of exclusivity, if the § 505(b)(2) application or ANDA contains a paragraph IV certification.
11 E.g., Orphan drugs are granted seven years of market exclusivity, new chemical entities (NCEs) are granted five years of market exclusivity, and older drugs that represent, e.g., a new use or a new dose are granted three years of market exclusivity. When pediatric studies are conducted at the request of the FDA, six months of additional pediatric exclusivity are provided. See, e.g., FDA: “Frequently Asked Questions on Patents and Exclusivity,” available online at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm (last accessed February 23, 2014).
13 Orphan drugs and biologics “are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.” See, e.g., FDA: “Developing Products for Rare Diseases & Conditions,” available online at http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm (last accessed February 23, 2014).
14 See the Food and Drug Administration Modernization Act of 1997, P.L. 105-115, § 505(A). Pediatric exclusivity is often additive to other exclusivity.

Continued on page 2...
The FDA is changing its definition of the term “drug,” which traditionally meant “drug product,” to mean “drug substance.” Thus, in evaluating a combination drug product for market exclusivity, the FDA now intends to re-interpret the law such that newly filed NDAs for new/old drug combinations will get five years (not three years as in the past) of market exclusivity, which will keep generics off the market for two additional years. Also, as a result of the FDA treating the new drug in new/old drug combinations as an NCE, ANDA/505(b)(2) application filers will have to wait until five years after approval to submit their applications (unless those applications contain paragraph IV certifications, in which case the applications can be submitted four years after approval). These provisions produce a windfall to brand manufacturers.

In altering its longstanding statutory interpretation, the FDA emphasized that new/old drug combinations are “increasingly prevalent in certain therapeutic areas” and that “these products play an important role in optimizing adherence to dosing regimens and improving patient outcomes.” The FDA was prompted to reconsider increasing market exclusivities of new/old drug combinations by Citizen’s Petitions submitted on behalf of Gilead Sciences, Inc., Ferring Pharmaceuticals, Inc., and Bayer HealthCare Pharmaceuticals, Inc. for the combination drugs Strioblend, Prepopik, and Natazia, respectively.

The petitioners argued that the FDA’s current policy prioritizes NDA submissions for single-ingredient drugs over NDA submissions for fixed-dose combination drugs, and that this “might lead to suboptimal drug development strategies, especially in light of the increasing importance of fixed-combinations.”

Additionally, the petitioners stressed that “limiting the order of approval to preserve exclusivity may not be available in some situations, such as for a new active moiety that may not be effective or safe unless it is marketed in a fixed-combination.”

Ironically, because the FDA intends to grant the additional market exclusivity only prospectively, drugs like Strioblend, Prepopik, and Natazia, which provided basis for the FDA’s reconsideration of the issue, would not be entitled to the additional exclusivity period.

Increased market exclusivities, which will take effect when the FDA finalizes the guidance, will be important to all organizations developing fixed-dose combination drugs. They also will be important to small, venture-backed pharmaceutical companies, as they can increase licensing royalties, company valuations, and post-merger or acquisition earn-outs. Finally, increased market exclusivities will affect the timing of the introduction of generic combination drug products.

Thus, strategies for developing and commercializing new/old drug combinations should be carefully reevaluated and optimized in light of the proposed new statutory interpretation that will grant five-year market exclusivity to these products.

For questions regarding market exclusivities, or any other related intellectual property or regulatory affairs matter, please contact David Hoffmeister, Vern Norviet, Samir Elamrani, Peter Munson, Stu Williams, T.O. Kong, Jeff Guise, Charles Andres, or any member of Wilson Sonsini Goodrich & Rosati’s patent and innovation strategies, life sciences, or global generics practices.