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Interchangeable Biosimilars–Time to Reform the Orange Book

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In 2011, generic drugs accounted for nearly 80% of all prescriptions filled by U.S. pharmacies. Yet, doctors prescribe generics by name in only about 10% of all prescriptions written, so what accounts for the high percentage of generic sales? The answer lies with state laws and health insurance policies that require prescriptions to be filled with ''therapeutically equivalent'' or ''A-rated'' generics (i.e. those listed in the Food and Drug Administration's Orange Book) whenever a brand is named. With ''interchangeable'' biosimilars soon coming to market, many have questioned whether the current system is capable of ensuring that these drugs will be properly dispensed in the same way. This begs the question: is it time to reform the Orange Book.

The Biologics Price Competition and Innovation Act (BPCIA) of 2009 introduced the concept of ''interchangeable'' biosimilars, which allows biologic drugs to be substituted for the brand without the intervention of a health care professional. This is similar to the Hatch-Waxman (H-W) concept of ''therapeutic equivalence,'' which confers substitutability of generic drugs for brand prescriptions, but with one important difference. Interchangeability of biologics is conferred on an indication-by-indication basis whereas therapeutic equivalence under H-W is routinely conferred for all indications. This means that when pharmacists, insurers and pharmaceutical benefits managers (PBM) decide to interchange a biosimilar for a pioneer biologic drug, they will be required to know what indication(s) the biosimilar was approved for and whether the doctor's prescription was intended to treat one of those indications.

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The Orange Book, which is used only for H-W approvals, does not provide ''substitutability'' information at the indication level so it cannot accommodate biosimilar approvals in its current form. Therefore, the FDA will have to modify its Orange Book or develop a new drug compendium to deal specifically with biosimilars and interchangeability.

A careful look at the issues suggests that Orange Book reform is the more compelling option. Not only will it unify the important prescribing information for both drugs and biologics, but Orange Book reform also will address a drug substitution issue that has plagued brand manufacturers for years. An example of this is the Orange Book's false designation of therapeutic equivalence for generic drugs that are not approved for all of the brand's indications (so-called ''skinny labeled'' generics) and which often omit certain safety information from the generic's label, putting patients needlessly at risk.

Bioequivalence for Small Molecules

Most small molecule generic drugs are approved under an Abbreviated New Drug Application (ANDA), which dispenses with the need to conduct extensive clinical testing on patients. Instead, the ANDA applicant is allowed to rely on the clinical trials conducted by the brand manufacturer provided the applicant can demonstrate that its product is ''bioequivalent'' to the brand (i.e. the reference listed drug). Under FDA rules,

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a generic drug is considered bioequivalent when the rate and extent of absorption of the drug (essentially, its ''bioavailability'') are not significantly different from that of the reference listed drug. The type of bioequivalency study depends upon the dosage form and route of administration (e.g. oral versus injectable), but generally the standards for proving bioequivalence are well established under FDA guidance documents and the United States Pharmacopoeia (USP). These include certain straightforward *in vitro* studies and *in vivo* biostudies and are generally straightforward and relatively inexpensive.

Traditionally, the FDA has allowed a bioequivalence study for one indication to suffice as proof of bioequivalence for all indications on the brand label, as long as the indications are ''related'' and involve the ''same site of action.'' *See, e.g., Graceway Pharms, LLC v. Sebelius*, 783 F. Supp.2d 104, 107 (D.D.C. 2011) (9 PLIR 603, 5/20/11). The FDA reasons that it can properly ''extrapolate'' bioequivalence under such conditions. Thus, a generic drug shown to be bioequivalent for one indication may be labeled for all approved indications and marketed as ''therapeutically equivalent'' or ''A-rated'' to the pioneer for the labeled indications.

Biosimilars and Interchangeability

On February 9, 2012, the FDA published the long-awaited guidance documents on the criteria for developing biosimilars for which an abbreviated approval pathway is envisioned under the BPCIA (10 PLIR 173, 2/10/12). Unlike the comparatively streamlined process for generic drug approval under Hatch-Waxman, approval for a biosimilar product, and especially a biosimilar that is considered ''interchangeable'' with the pioneer product, will involve a more rigorous undertaking.

The FDA has proposed a ''stepwise'' approach to demonstrating biosimilarity for a specific condition of use, starting with extensive structural and functional characterization of the proposed and referenced product and followed by animal and clinical studies. Since biological products are comparatively more complex than small molecule drugs, the FDA envisions characterizing any differences between biosimilar and reference pioneer products through structural characterization comparing the primary structure, higher order structure, enzymatic post-translational modifications, and other potential variants, with special attention to differences as a result of variations in the manufacturing process. The functional characterization will involve showing that the biologic activity and potency of the proposed product are highly similar and/or there are no clinically meaningful differences. One aim of these assays is to demonstrate that the mechanism of action of the biosimilar product is the same as that of the reference product.

After structural and functional characterization, the FDA proposes that the applicant conduct animal studies, including animal toxicity studies, and pharmacokinetic (PK) and pharmacodynamics (PD) studies, which can be incorporated into a single animal toxicity study if appropriate. The applicant will also generally be required to conduct clinical studies sufficient to demonstrate safety, purity, and potency for the intended use.

To meet the higher standard of ''interchangeability,'' an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. *See* section 351(k)(4) of the Public Health Service Act (PHS). Interchangeable biosimilars may be substituted for the reference product without the intervention of the prescribing healthcare provider. *See* section 351(i)(3) of the PHS Act.

The FDA guidelines indicate that an interchangeable biosimilar may be licensed (i.e. approved by the FDA) for one or more additional conditions of use for which the reference product is approved provided the applicant can provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each additional condition of use. Although biosimilar manufacturers will, undoubtedly, seek to be approved for all indications for which the pioneer drug is approved, it is not clear what criteria will be required to support the extrapolation of clinical data to include indications that were not studied in the biosimilar application. The more likely scenario may be biosimilar products may be approved, at least initially, with ''limited'' substitutability for the reference product, i.e. only for the indications for which approval was specifically obtained. This, however, presents problems for those who advocate using the Orange Book as the official source of interchangeable biosimilars.

The Problem With the Orange Book

The FDA's Orange Book, which actually pre-dates Hatch-Waxman by four years, provides doctors, pharmacies and reimbursement agencies with important information about pioneer drugs and their generic equivalents. A generic drug found to be ''therapeutically equivalent'' to a pioneer drug is given an ''A-rating'' in the Orange Book and deemed fully substitutable for the pioneer. The Orange Book also contains information on pioneer drug exclusivity rights and patents that protect the drug product and methods of using the drug.

If a generic manufacturer seeks approval to market a copy of a pioneer drug for fewer than all the approved indications–for example, to avoid infringing a method of use patent listed in the Orange Book–it can seek to omit such indication from its label by filing a ''section viii'' statement in place of a patent certification. In this way, the generic applicant is permitted to ''carve-out'' potentially infringing use(s) from the label but, in turn, agrees not to market its drug for those carved-out uses.

The FDA must also find that the generic drug, with the patented information omitted from its label, is as safe and effective as the pioneer drug for all remaining non-patent protected conditions of use. Thus, if the FDA allows an indication to be carved out, the generic drug is approved with an A-rating in the Orange Book, even though it will not contain all of the approved uses as the pioneer and may be missing critical safety information associated with the carved out use.

For example, if a brand name drug is approved for treating medical conditions ''A'' (patent protected) and ''B'' (not patent protected), a generic applicant can carve indication ''A'' out of its label to avoid infringe-

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ment; however, it must also omit all safety and efficacy data associated with indication ''A'' to obtain FDA approval. This now becomes a ''skinny labeled'' generic because its label omits information contained on the brand label. Subsequently, a patient who is made to take the skinny labeled generic in place of the brand under state substitution laws or insurance policies, may end up taking the generic to treat indication ''A,'' but without the required information on how to take the drug safely and effectively for that indication.

This happens regularly with all skinny labeled generics. Physicians, state pharmacies and health insurance companies have no way of knowing what indications have been carved out from the brand labels because the FDA does not publish such information in its Orange Book or elsewhere. Doctors write prescriptions for brand name drugs without reference to the indication or condition being treated; thus, there is no way for a pharmacist to determine what condition the drug is intended to treat when the substitution decision is being made. This means that the ''blind'' substitution of skinny labeled generics for branded drugs not only results in the infringement of pioneer patents but also puts the patient at risk if safety and efficacy information has been omitted from the generic labels.

Although the current Orange Book system has largely been tolerated for small molecule drugs, it obviously needs restructuring to work for interchangeable biosimilars because these must be tested and approved on an indication-by-indication basis. If done right, it could also address the skinny labeled generic ''problem'' discussed above. Such a system, for example, could easily inform the public that certain brand indications have been carved out of generic labels so that pharmacists and others would be on notice that certain uses are not just patent protected but that the generic is not safely and effectively labeled for such uses. There are currently over two dozen brands that are skinny labeled by generics with annual sales for carved out uses estimated to be well over $1 billion.

A single Orange Book listing system for both small molecule and biological products would benefit the entire health care industry. It would function as a source of information for interchangeable biosimilar products under the BPCIA and provide doctors, pharmacists and insurers with essential patent and safety information before generic/biosimilar substitution decisions are made.