

## Generic Drugs, Part 2: Current Controversies

### Introduction

In February, we started a discussion about generic medications by outlining a brief history of significant legislation that governs the generic approval process utilized by the Food and Drug Administration (FDA). That article was intended to provide a basic understanding of the concept of bioequivalence which allows the FDA to approve low-cost alternatives to expensive BRAND NAME products once they have lost their patent protection. This is an important discussion since generic drugs now account for 70 percent of all prescriptions in the United States. Health plans, third party payers and pharmacy benefit managers promote these less costly, bioequivalent medications as a way to reduce health care costs and to facilitate patient access to important treatments. At the same time generics represent only about 18-20 percent of the total health care expenditures for pharmaceuticals. Controversies, however, surround the utilization of these low-cost alternatives. Examples of current issues that require further discussion include: a) Narrow-Therapeutic Index medications, b) "Pay for Delay" settlements, and c) the search for a generic approval process for high-tech bio-similar medications.

### Narrow-Therapeutic-Index Medications (NTI):

A medication is said to have a "narrow therapeutic index" or "therapeutic window" when the serum levels required to exert its desired clinical effect are also close to levels associated with toxic side effects. As a consequence, in order to utilize these medications in a safe and effective manner physicians usually need to follow careful dose titration and regular patient monitoring. Despite well-documented determinations of statistical bioequivalence, opponents of generic substitution for certain therapeutic drug classes (e.g. immunosuppressants, anticonvulsants, warfarin, digoxin, lithium, etc.) continue to raise questions about changes in efficacy and toxicity and have voiced the need for patients to receive consistent products with routine refills. In fact, most experts will warn that the real problem is the switching between generic products as opposed to switching between a generic and a brand since bio-equivalence testing is between the brand and a generic—NOT between generics. Adding to the public fear of generic alternatives is a wave of anti-generic claims in consumer publications and television programs that feature patient complaints about significant adverse reactions to generic therapies. "Carve-out" laws and regulations that limit generic substitution at the pharmacy (e.g., dispensing of AB-rated generic products for NTI branded drugs) vary widely by states. For example, in North Carolina, state law requires that the pharmacist dispense the same drug product from the same manufacturer for each refill of a NTI medication. Documented prescriber and patient consent must also be received prior to any switch in products. California and Texas, on the other hand, have no special regulations when considering the substitution of brand name NTI products for a generic alternative.

### 'Pay for Delay' Settlements:

Another controversy regarding the approval of generic medications involves efforts by the pharmaceutical industry to either delay or undermine the generic medication approval process. One such effort is the use of "authorized generics." An authorized generic exists when a pharmaceutical manufacturer sells a drug under both a brand name and a generic label. Since authorized generics are considered brand products by the FDA, the authorized generic does not have to go through the same rigorous, Abbreviated New Drug Application (ANDA) approval process required by a true generic. As noted in the February article, the first generic competitor of a branded drug product is awarded a 180-day period of marketing exclusivity under the Hatch-Waxman Act in an effort to help "first filers" recoup expensive legal fees. Unfortunately, it does not preclude competition from an authorized generic. Authorized generic entry during this time can substantially reduce the revenues of a first-filer generic firm by 47 to 51 percent as reported by a recent Federal Trade Commission (FTC) report. As a result, a generic firm may be willing to agree to defer its market entry in return for a brand manufacturer's promise not to launch a competing authorized generic during the 180-day marketing exclusivity period. An example of this practice involves the release of an authorized generic for PROTONIX (pantoprazole). Such practices can harm consumers in two ways: First, generic drugs and the accompanying price discounts would not be available to consumers as soon as would otherwise have been the case. Secondly, consumers would lose the benefit of price discounts from the authorized generic competition during the 180-day exclusivity period. The FTC report also states that between fiscal years 2004 – 08, about 25 percent of the final patent settlements reviewed by the FTC contained provisions related to authorized generics and an agreement by the brand manufacturer not to launch an authorized generic to compete against the first-filer combined with an agreement by the first filer to defer entry past the settlement date by an average of 34.7 months. The FTC has gone to court to block delay settlements and congressional leaders may try and curb these deals through legislation (e.g., HR 573).

### **Battle over Bio-similars:**

With procedures for developing and marketing generic drugs well established, generic manufacturers are naturally looking for expansion in the manufacture of more complex dosage forms such as biologic agents, commonly known as “bio-similars” or follow-on biologics (FOBs). Examples of this class of medications include REMICADE (infliximab) and ENBREL (entercept) which are used to treat rheumatoid arthritis. These agents, few of which existed in 1984, include many important new therapies and constitute the fastest growing segment (25 percent of total pharmacy costs in 2008) of the pharmaceutical market. As promising as these therapies appear to be, their costs can be substantial, reaching \$200,000 or more annually for treatments such as imiglucerase (CEREZYME) which is used to treat Gaucher’s Disease. Consumer protection groups, health insurers, and pharmacy benefits managers (PBMs) have supported a five-year period of exclusivity promoted by Rep. Henry Waxman (D-CA). Manufacturers would argue that added protection from competition is fair, based on the fact that development costs for biologic products are so much higher than for other medications. Generic manufacturers and consumer groups argue that it would discourage development of generic biologics and reduce the incentive to develop new products. Even the FTC has weighed into the debate with a study that states that introduction of bio-similars would lower costs to consumers without hampering drug innovation and development. Industry analysts say that if the law changes to allow bio-similar drugs, the FDA can expect a lot of approval requests. Many biotech drug patents have either expired or will expire in the next 5 to 10 years. When that happens, experts expect bio-similars to cost 20 to 30 percent below the cost of brand name products. Ultimately, FOBs are a balancing act for lawmakers—balancing the need to control escalating specialty drug costs while making sure it doesn’t come at the expense of future new drug research and development.

### **What can we expect from Health Care Reform?**

Recently, passage of the Healthcare Reform bill in Congress resolved a number of related issues—at least for the foreseeable future. The Health Care and Education Reconciliation Act of 2010 (H.R. 4872) would authorize the FDA to create an approval pathway for FOB products that would guarantee manufacturers 12 years of market exclusivity before any bio-similar product could be approved, even in the absence of a valid patent. In addition, manufacturers could also obtain additional 12 year exclusivity by making minor changes to the structure of an approved product, such as those that could lead to changes in its administration schedule. It remains to be seen how the new law pertains to older products with expired patents. On the other hand, efforts by consumer groups, senators, and even President Obama to add a “Pay-for-delay” provision to the Senate health care bill have failed. The provision, which was based on a bill (S. 369) introduced by Sen. Herb Kohl (D-WI) in February 2009, would have prohibited payments from brand name to generic drug manufacturers with the purpose to prevent or delay the entry of competition from generic drugs.

### **Conclusion:**

In spite of some continuing controversies outlined above, the utilization of generic drug products continues to grow as more products become available and as consumers, private health plans and government programs look for alternatives to increasingly expensive brand name products. Generic drugs represent a valuable alternative for those patients with no insurance, or even those with insurance who face increasing financial co-sharing responsibility. Studies continue to show that drug costs can be a significant factor to determine a patient’s adherence to therapy, even when the patient has health insurance. Lastly, because beneficiaries in the Medicare Part D program are currently liable for up to \$4,550 in out-of-pocket expenses before Catastrophic Coverage takes effect, seniors are increasingly turning to generic drugs in an attempt to lower their monthly drug bills.

### **References:**

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