



## Generic Drugs, Part 1: The Approval Process

### Introduction

The availability of generic alternatives continues to expand as former blockbuster brand name products lose their patent protection. Generic drugs now account for 70 percent<sup>1</sup> of prescriptions in the United States as health plans, third-party payers and pharmacy benefit managers promote these less costly, bioequivalent medications as a way to reduce health care costs and facilitate patient access to important treatments. Conversely, generics represent only about 18 to 20 percent of the total health care expenditures for pharmaceuticals. On average, the cost of a generic drug is 80 to 85 percent lower than the brand name product it replaces. Utilizing our own BCBSIL claims data, the average ingredient cost of generic prescriptions decreased 6.8 percent as opposed to a 50.3 percent increase in brand name medications during the first four years (1<sup>st</sup> Quarter 2006 – 4<sup>th</sup> Quarter 2009) of the Medicare Part D program.

On a national level, the average price for branded products continues to rise at a much faster rate than the Consumer Price Index (CPI). In a recent article,<sup>2</sup> pharmaceutical manufacturers were seen raising prices by an average of 9 percent in 2009 (CPI 2009 = 2.7 percent) on their products for the steepest increase since the passage of the Medicare Part D legislation in December 2003. Some notable examples of highly utilized brand name drugs which are now available generically due to a loss of patent protection in 2009 include: DEPAKOTE ER, TOPAMAX, CELLCEPT, and PREVACID. Anticipated in 2010 are generic equivalents for FLOMAX, COZAAR/HYZAAR, ARMIDEX, AMERGE and EFFEXOR XR. Lastly, while direct out-of-pocket savings represent a significant advantage for generic medications, studies have also shown important trends in indirect costs such as improvements in therapy adherence that can lead to improved outcomes.<sup>3</sup>

### Legislative History of Generic Drug Industry<sup>4</sup>

The U.S. Food and Drug Administration (FDA) defines a generic drug as a product that compares, within closely defined parameters, to the pioneer, or reference drug product, in dosage form, route of administration, strength, quality, safety and performance characteristics. The generic drug must have the same intended uses as the pioneer product that serves as its prototype. Below is a list of significant legislation that has affected the regulation, manufacture and marketing of generic products:

- **Pure Food and Drug Act of 1906:** The passage of the Pure Food and Drug Act of 1906 was the first attempt by the federal government to require product labeling in an effort to prevent the introduction of misbranded and adulterated food and drugs into interstate commerce.
- **Food, Drug, and Cosmetic Act of 1938:** Responding to the “sulfanilamide disaster” of 1937 that resulted in 107 fatalities, Congress designated products introduced after 1938 as new drugs and required them to be proven safe through manufacturer testing and FDA clearance before being marketed. This was the beginning of the approval process for drugs in the United States; that is, the process of requiring the submission of a New Drug Application (NDA). Unfortunately, the Act did not require the manufacturer to prove effectiveness of the product and also exempted pre-1938 drugs from meeting the FDA’s pre-approval requirements.
- **Kefauver-Harris Amendment of 1962:** The Kefauver-Harris Amendment established the current pre-market approval process by requiring the manufacturer to establish a product’s safety and effectiveness prior to marketing. It also required manufacturers of related products to submit an Abbreviated NDA (ANDA) for products marketed between 1938 and 1962.
- **Drug Price Competition and Patent Restoration Act of 1984 (Hatch-Waxman):** This important piece of legislation, commonly referred to as the Hatch-Waxman Act, was passed to balance the competing forces of generic and innovator drug firms by creating a more equitable process for approving generic drugs. Under the new ANDA procedures outlined in the Act, a therapeutically equivalent generic post-1962 drug can be marketed if FDA bioequivalence requirements for approval are met and the manufacturer follows FDA Good Manufacturing Practice (GMP) regulations and labeling requirements. The Act also establishes a process for manufacturers of branded products to extend the term of their patent by partially offsetting time spent in the FDA NDA review process and in clinical testing. The average length of patent-term extensions granted under this provision is three years. Lastly, a generic drug can also gain some market exclusivity under the Hatch-Waxman Act. Since a generic manufacturer may face the cost of patent litigation under these circumstances, the Act provides an incentive by granting the first company (“first filer”) to file an ANDA with a patent challenge, a 180-day exclusive marketing period.

**Bioequivalence:**

As noted above, the approval process for generic drugs allows use of the ANDA, which does NOT require submission of clinical data supporting safety and efficacy since this information was already provided for the pioneer product. In order to receive approval for marketing, however, a generic drug must meet the same batch manufacturing requirements for identity, strength, purity and quality, and must be **therapeutically equivalent** to the branded product. For the generic drug to be therapeutically equivalent, two clinical characteristics must apply: It must be a) pharmaceutically equivalent, as well as b) bioequivalent.

**Pharmaceutical equivalence** means that the active ingredient(s), dosage form, route of administration, and strength are the same for both the generic and brand name product although they do not need to contain the same inactive ingredients. **Bioequivalence** occurs when both products have comparable bioavailability (i.e., rate and extent of absorption) when studied under similar conditions.

While the concept of pharmaceutical equivalence is easy to comprehend, understanding the concept of bioequivalence is a bit more complicated. Bioequivalence involves the determination and comparison of serum drug concentrations (e.g., AUC = area under the concentration curve, C<sub>max</sub> = maximum serum concentration, etc.) between the generic and branded products. The identical criteria applied to testing for bioequivalence of branded products undergoing reformulation or other manufacturing changes (e.g., moving drug production to alternative manufacturing site, etc.) is required to determine bioequivalence of generic products. A variance of greater than 10 percent from the FDA criteria disqualifies a drug from a bioequivalence rating. A recent article that looked at data from 2,070 single dose clinical bioequivalence testing performed by the FDA between 1996 to 2007 found the mean variation in C<sub>max</sub> and AUC between branded and generic drug products was 4.35 percent and 3.56 percent, respectively.<sup>5</sup> Lastly, another study evaluated the results of 38 published clinical trials that compared generic cardiovascular drugs to their brand name counterparts. The author's conclusion was that there was no evidence to support brand-name cardiac medications performed any better than the generic alternatives.<sup>6</sup>

The FDA source for therapeutic equivalence is titled the *Approved Drug Products with Therapeutic Equivalence Evaluations*, but is more commonly known as the "Orange Book." The Orange Book uses a two-letter coding system for the therapeutic equivalence evaluations of multi-source drug products. The first letter is either an A or B. Products rated with the first letter A are considered therapeutically equivalent to a reference drug product, while products with the first letter B are not, for a variety of reasons. The second letter of the rating often refers to specific dosage forms or other product features. For example, a generic drug that was AB rated would be considered bioequivalent to the FDA reference drug (e.g., lisinopril – ZESTRIL). Lastly, a common misconception related to therapeutic equivalence is that while generic products may be considered bioequivalent (or AB rated) to a branded drug, there is no testing to determine whether generic products are bioequivalent to each other, although it would be expected that their efficacy would not differ significantly.

**Conclusion:**

The purpose of this article is to provide background information on the current approval process for the marketing of generic medications and to assist prescribers in making informed decisions when ordering generic products for their patients. This background information will be helpful in understanding some of the current controversies involving generic drugs that will be detailed in a follow-up article. Look for this article in the next few months. Topics will include: Narrow-Therapeutic Index medications, "Pay for Delay," and the difficulty in developing an FDA approval process for high-cost, high-tech biologics.

**References:**

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