

# The FDA's Generic-Drug Approval Process: Similarities to and Differences From Brand-Name Drugs

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## Introduction

Once patent exclusivity of a brand-name drug expires, an application for generic-drug approval can be submitted to the US Food and Drug Administration (FDA) (1,2). The FDA publishes a list of brand-name drugs whose patent protection has expired in “Approved Drug Products With Therapeutic Equivalence Evaluations,” commonly known as the Orange Book (3). It identifies drug products approved by the FDA for safety and effectiveness that are considered pharmaceutical equivalents when administered to patients under conditions specified in the drug’s labeling. We review similarities and differences between the FDA’s approval processes for generic and brand-name drugs.

## Similarities between generic and brand-name drugs

Generic drugs are essentially the same as brand-name drugs, with regard to intended indication/use, active ingredients, dosage form and strength, route of administration, safety, quality, performance, purity, and stability. The FDA classifies generic drugs as therapeutically equivalent to brand-name drugs when the products

have been determined to be safe and effective for a specific indication and are considered to be pharmaceutically equivalent, i.e., they contain identical amounts of the same active drug ingredient, in the same dosage form and route of administration, and meet US Pharmacopeia (USP) compendia standards. The generic drug must be bioequivalent to the brand-name drug, be adequately labeled for proper use, and be manufactured in compliance with current good manufacturing practice (GMP) regulations. The FDA considers drugs therapeutically equivalent even though they may differ in characteristics such as tablet shape, scoring, packaging, excipients (e.g., colors, flavors, and preservatives), and expiration dating or storage conditions. Although such differences may be important in the care of a particular patient, and it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity, the FDA believes that products classified as therapeutically equivalent can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

In general, the FDA approval applications for both generic and new brand-name drugs are required to provide detailed information on the product’s chemistry, manufacturing steps, and quality control measures, as well as compliance with federal regulations for current GMP (4). Manufacturers of both generic and brand-name drugs are required to demonstrate evidence of the drug’s stability, as indi-

cated on the product label, and maintain ongoing monitoring of the drug’s shelf life. Detailed chemistry, manufacturing, and control (CMC) information is required for both the drug substance (active ingredient), e.g., omeprazole, and the drug product (final drug form administered to the patient), e.g., Prilosec, which includes all of the inactive components used in the final drug product. Drug manufacturers are also required to evaluate whether the drugs or the manufacturing process, including any waste discharge, will have any environmental impact, and to have a plan to mitigate it. Likewise, the raw materials and finished products of both generic and brand-name drugs are required to meet USP compendia specifications of strength and quality (5). The USP is a nongovernmental, official public standards-setting authority for prescription and over-the-counter medicines manufactured or sold in the United States. The Food, Drug, and Cosmetic Act of 1938 requires that all prescription and over-the-counter medicines sold in the United States comply with quality standards published in the USP National Formulary. Ultimately, these FDA requirements result in drug product labels for both generic and brand-name drugs that are indistinguishable.

## Differences between generic and brand-name drugs

A brand-name drug is supplied by one company and sold under a trademarked name, e.g., Prilosec. Generic drugs may be supplied by more than one company and sold under the name(s) of the active ingredient(s), e.g., omeprazole. An

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**Table 1. Commonly prescribed FDA-approved generic gastrointestinal drugs**

Generic name	Brand name
Atropine	Atropen
Atropine/diphenoxylate	Lomotil
Azathioprine	Imuran
Balsalazide	Colazal
Calcium acetate	PhosLo
Cholestyramine	Questran
Cimetidine	Tagamet
Cyclosporine	Sandimmune
Dicyclomine	Bentyl
Dronabinol	Marinol
Famotidine	Pepcid
Glycopyrrolate	Robinul
Granisetron	Kytril
Hyoscyamine	Levsin
Hyoscyamine extended-release	Levbid, Levsinex
Lactulose	Constulose
Lansoprazole	Prevacid
Loperamide	Imodium
Meclizine	Antivert
Mesalamine enema	Rowasa
Methylprednisolone	Medrol
Metoclopramide	Reglan
Misoprostol	Cytotec
Nizatidine	Axid
Octreotide	Sandostatin
Omeprazole delayed-release	Prilosec
Ondansetron	Zofran
Pantoprazole delayed-release	Protonix
Polyethylene glycol 3350	NuLytely
Prochlorperazine	Compazine
Promethazine	Phenergan
Ranitidine	Zantac
Sucralfate	Carafate
Sulfasalazine	Azulfidine
Ursodiol	Actigall

application for a brand-name drug must include evidence showing the drug can be safely used and is effective in the proposed patient population. Such evidence may require testing in hundreds of animals and the treatment of tens of thousands of patients before a brand-name drug can be approved by the FDA. A generic-drug application, however, does not have to demonstrate any preclinical or clinical safety or efficacy data in the intended patient population but need only demonstrate bioavailability and bioequivalence to the brand-name drug. To be considered bioequivalent to a brand-name drug, the generic drug must show similar bioavailability, defined as rate and extent of

absorption, when studied under conditions similar to those used with the reference brand-name drug. This is usually demonstrated in small clinical studies with normal human volunteers. Bioequivalence is determined by a variety of means, including pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and/or *in vitro* studies.

A manufacturer applying for FDA approval of a brand-name drug must conduct a series of animal and *in vitro* studies evaluating the pharmacology and toxicology of the drug before opening an investigational new-drug application to conduct human clinical studies. Subsequently, adequate, well-controlled clinical studies

are necessary to demonstrate the safe and effective use of the drug in the planned patient population. In general, these clinical studies include clinical safety, pharmacokinetic, and bioavailability studies in healthy human volunteers (phase I studies); proof-of-concept studies showing the drug may be effective in treating the specific disease (phase IIa studies); dose-ranging studies to define the lowest effective dose (phase IIb studies); and large, well-controlled studies evaluating drug safety and efficacy (phase III studies). The number of clinical studies needed for approval varies by therapeutic indication and availability of other adequate treatments for the disease (6).

FDA approval of generic drugs requires the applicant drug company to supply the proposed drug label, CMC information (6), and bioavailability and bioequivalence data for the generic drug. A side-by-side label comparison of the generic and brand-name drugs is required in the application, with any differences in labels annotated and justified.

The Drug Price Competition and Patent Term Restoration Act of 1984 provides the FDA with legal authority to approve generic drugs using adequate bioavailability and bioequivalence data (7). The Code of Federal Regulations defines bioavailability and bioequivalence requirements for generic-drug market approval (8). In an effort to further interpret both this Code and the 1984 law, the FDA issued a document in 2003 entitled “Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations” (9). This document provides guidance for the requirements and process that a drug company must follow when applying for generic-drug market approval. The 1984 law, the Code of Federal Regulations, and the 2003 FDA guidance document all require that for a generic drug to be approved for sale to the public, the drug company must provide bioavailability data, and the FDA must conclude the drug is bioequivalent to a brand-name drug (7–9).

Bioavailability studies are conducted in a small number of normal adult volunteers to evaluate the performance of the

drug. These studies may be conducted throughout the generic-drug formulation development program, as the formulation is being optimized for comparability to the brand-name drug. The most common method for demonstrating bioequivalence between a generic drug and the reference brand-name drug is a single-dose, two-treatment, crossover-designed pharmacokinetic study in normal adult volunteers. Single doses of each drug are administered in the fasted state, and blood or plasma levels are measured over time. The primary pharmacokinetic measurements to demonstrate bioequivalence are the area under the plasma concentration curve (AUC) for measurement of the extent of absorption and the maximum drug concentration (C<sub>max</sub>) as a measure of the rate of the drug's absorption.

Bioequivalence studies must show that the generic drug has a pharmacokinetic profile similar to that of the brand-name drug. For FDA approval, a generic-drug manufacturer must show that the 90% confidence intervals for the ratio of the mean response of the AUC and C<sub>max</sub> of its product are within 80–125% of those of the brand-name drug, with a significance level of  $P < 0.05$ . It is important to note that the confidence intervals for generic drugs can be as low as 80% and as high as 125% of those for the brand-name drugs, with regard to the rate and overall exposure of the drug in humans. For most generic drugs, this variation is not an issue; for some drugs with a narrow therapeutic index or critical dose, it could prove problematic, as patients may experience toxic reactions to higher-than-expected dose levels. Stricter bioequivalence standards were recently recommended but have not yet been endorsed by the FDA (10).

Currently, the bioequivalence standards for generic drugs have been developed for orally administered drugs that act systemically (9). For oral drugs that act locally, e.g., in the gastrointestinal tract, FDA guidance suggests that a generic orally administered drug be considered bioequivalent to a brand-name drug by the use of clinical safety and efficacy studies and/or validated *in vitro* studies.

### Examples of gastrointestinal generic drugs and the generic-drug approval process

**Table 1** lists commonly prescribed FDA-approved generic gastrointestinal drugs (3).

In 2002, the FDA approved the new drug application of Kremers Urban Development Company (KUDCo) for 10-mg and 20-mg Omeprazole Delayed-Release Capsules. This approval allowed for a generic omeprazole product to compete with AstraZeneca's Prilosec for the treatment of gastrointestinal conditions. KUDCo's application was based on three small clinical studies in healthy volunteers: two single-dose bioequivalence studies, under fed and fasting conditions ( $n = 46$ ), and one single-dose bioavailability study ( $n = 21$ ) comparing the pharmacokinetics of the generic 20-mg delayed-release capsule with that of the AstraZeneca 20-mg Prilosec product. The results of all three studies showed that the generic product was bioequivalent to the brand-name drug, with the AUCs being between 88% and 98% (90% confidence interval) and the C<sub>max</sub> values being between 98% and 116% of those of the brand-name drug in the fasting study.

In 2004, the FDA approved a generic mesalamine rectal suspension 4 g/60 ml enema made by Clay-Park/Perrigo and determined that the product was bioequivalent to the Rowasa rectal enema, made by Solvay, for the treatment of mild to moderate ulcerative colitis. The approval was based on one two-way single-dose crossover-designed bioequivalence study of 47 normal volunteers that compared the pharmacokinetic parameters of the generic product with those of the brand-name drug. Although the drug is believed to act locally, the approval was based on measurement of plasma mesalamine (5-aminosalicylic acid) levels. The study demonstrated that the generic-drug AUCs of 85–124% (90% confidence interval) and C<sub>max</sub> values of 95–120% were within the FDA guidelines and therefore deemed the generic drug to be bioequivalent to the brand-name drug.

### Summary

Generic and brand-name drugs are similar in terms of their intended indication/use, active ingredients, dosage form and

strength, route of administration, safety, quality, performance, purity, and stability. Generic drugs may differ in shape, scoring configuration, release mechanisms, packaging, excipients (colors, flavors, preservatives), and product expiration. If drugs with such differences are substituted for each other, there is a potential for patient confusion.

The main difference between generic and brand-name drugs is the amount and type of evidence supporting the market application of the respective drug. A brand-name drug is required to demonstrate substantial preclinical and clinical evidence showing safety and efficacy in a patient population. A generic drug does not have to demonstrate this safety or efficacy, as it is assumed the drug will act in a similar manner. However, a generic drug is required to demonstrate bioequivalence to the brand-name drug.

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### CONFLICT OF INTEREST

**Guarantor of the article:** Arthur A. Ciociola, PhD.

**Specific author contributions:** The FDA-Related Matters Committee of the American College of Gastroenterology identified the need and developed the concept for this article. Arthur A. Ciociola was the primary author and wrote the first draft of the manuscript. Costas H. Kefalas reviewed and revised the final manuscript, incorporating edits from members of the ACG FDA-Related Matters Committee.

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