

## GENERIC DRUGS

When patents expire on brand-name drugs and generic formulations become available, patients and managed care organizations may express a preference for the lower-cost generics. Are they equivalent to the brand-name product?

**MANUFACTURERS** — Comparatively inexpensive generic drugs are marketed both by generic drug companies and by manufacturers of well-known brands. Lederle, for example, markets generic methotrexate. Abbott makes both brand-name and generic formulations of erythromycin. Many brand-name manufacturers own generic companies. Novartis, for example, owns Geneva and Apothecon. Schering-Plough owns Warrick.

**FDA RATINGS** — The US Food & Drug Administration has rated all generic drugs "A" or "B" ([www.fda.gov/cder/ob/default.htm](http://www.fda.gov/cder/ob/default.htm)). "A" drugs are considered bioequivalent to the brand-name original. They either have been demonstrated to be so by human bioavailability study ("AB"), or are considered inherently unlikely to have bioavailability problems ("AA"); "AA" drugs are usually oral solutions or oral drugs that dissolve readily in water. Other "A" designations (AN, AO, AP, AT) refer to non-oral formulations considered bioequivalent by the FDA. Only "A" rated products are interchangeable with their brand-name equivalents by the FDA.

"B" drugs have not been demonstrated to be bioequivalent by an *in vivo* test. These are generally older drugs that were approved by the FDA on the basis of chemistry, manufacturing controls and *in vitro* dissolution tests. Less than 3% of marketed generic drugs have a "B" rating. The table below lists all drugs that currently are rated "B." A few of these drugs may be available in one or more formulations that have been given an "A" rating.

**IN VIVO BIOEQUIVALENCE TESTS** — The bioequivalence of generic drugs is typically tested by giving a single oral dose to 24 to 36 healthy human volunteers. The 90% confidence intervals for the peak serum concentration ( $C_{max}$ ) and area under the plasma concentration-time curve (AUC) of a generic formulation must fall within 80% to 125% of those of the brand-name drug. Mean AUC values are typically within about 3% of each other. With some older drugs, such as phenytoin (*Dilantin*, and others), the generic manufacturers' main challenge was to make a generic that was absorbed as poorly as the brand-name original.

**THERAPEUTIC EQUIVALENCE** — Product recalls for potency problems occur with both generics and brand-name products. No well-documented therapeutic differences between brand-name originals and FDA-approved generics have been reported. Some drugs, such as carbamazepine (*Tegretol*, and others), have inherent bioavailability problems; loss of seizure control and drug toxicity have been reported with both generics and the brand-name original.

**BIOGENERICS** — Several widely used biologicals (*Epogen*, *Neupogen*, *Avonex*, *Intron A*, etc.) will lose their patent protection over the next few years. Biogenerics are already marketed in some parts of Eastern Europe, but guidelines for biogeneric

approval have not been established in the US. If drugs manufactured by generic biotech companies have to go through the same testing process as the innovator drug, the cost savings usually associated with generic drugs will largely be cancelled out.

**CONCLUSION** — FDA-approved generic drugs with "A" ratings are bioequivalent to brand-name products. "B"-rated generic drugs may also be bioequivalent to the brand-name original, but have not been shown to be so. Well-documented therapeutic inequivalence between brand-name and FDA-approved generic drugs has not been reported.

### "B"-RATED DRUGS\*

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Amitriptyline hydrochloride/Perphenazine tablets	Medroxyprogesterone acetate tablets
Chlorpromazine hydrochloride tablets	Methyltestosterone tablets
Chlorthalidone tablets	Morphine sulfate extended-release tablets
Clindamycin phosphate gel	Nortriptyline hydrochloride capsules
Clotrimazole topical cream	Penicillin G benzathine injection
Colchicine/Probenecid tablets	Phendimetrazine tartrate extended-release capsules
Cortisone acetate tablets	Phytonadione injection
Cyclosporine capsules and solution	Prednisolone tablets
Dexamethasone tablets	Promethazine hydrochloride tablets
Diflorasone diacetate topical cream	Promethazine hydrochloride rectal suppositories
Diltiazem hydrochloride extended-release capsules	Propranolol hydrochloride tablets
Dyphylline tablets	Propylthiouracil tablets
Fluoxymesterone tablets	Quinidine gluconate extended-release tablets
Fluphenazine hydrochloride tablets	Reserpine tablets
Glyburide tablets	Theophylline extended-release capsules and tablets
Hydrocortisone tablets	Tretinoin gel
Ibuprofen suspension	Triamcinolone tablets
Iron Dextran injection	Trichlormethiazide tablets
Isosorbide dinitrate tablets	Verapamil hydrochloride extended-release tablets
Leucovorin calcium tablets	

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\* Includes generic and second or subsequent brand-name drugs.