
Oklahoma Health Care Authority

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Drug Utilization Review for Oklahoma Medicaid

The Myths & Facts about Generic Drugs: What do you know?

As healthcare costs continue to spiral upward, much attention has been focused on a single component that is believed to be a primary contributing factor to this dilemma—*pharmaceutical expenditures*. Oklahoma Medicaid has realized 15 to 20% annual increases in this area over the last couple of years. Health maintenance organizations, third party insurers, and the healthcare industry as a whole have made various efforts to reduce drug expenditures. These cost-containment measures have included formulary design and management, changing copayment structures and encouraging the use of generic medications. Substitution of FDA-approved generic products remains a very useful method to decrease national healthcare gross expenditures. According to a study conducted by the National Consumer's League, overall generic utilization in 1998 was 41% yet accounted for only 8% of total dollars spent on prescription drugs.¹ The Congressional Budget Office also reported that generic drugs could save consumers an estimated \$8 to \$10 billion a year at outpatient pharmacies and substantially more in hospital institutions.² Generic medications can provide a safe, effective and less expensive alternative for patients. Despite their obvious advantages, generic medications continue to be underutilized on a national level.



Healthcare professionals may harbor certain doubts about the efficacy and safety of generic drugs. Misconceptions exist regarding manufacturing standards, variations in the rate and extent of absorption, and differences in clinical and physiological outcomes for generic drugs relative to the innovator product.^[3, 4] These concerns have formed an effective barrier preventing providers from advocating generic substitution. But what is the validity surrounding these issues?

The FDA Approval Process: NDA vs. ANDA

A New Drug Application (NDA) must first be filed with and approved by the FDA before a pharmaceutical company can distribute and market an innovator medication. The NDA documents the safety and efficacy of the medication and the manufacturing control procedures to be used in the production of the medication.^[2, 5, 6] The research and developmental (R&D) process necessary to ascertain an approval for a new drug entity is extremely costly and may take many years. Furthermore, the majority of a medication's patent life has elapsed during the testing and evaluation period, leaving the manufacturer a limited amount of time to recover their R&D costs.⁷

In contrast, generic drug companies must only file an Abbreviated New Drug Application (ANDA). To gain FDA approval of an ANDA, a generic drug must:

- contain the same active ingredients as the innovator drug (inactive components may vary)

- be identical in strength, dosage form, and route of administration
- have the same use indications
- be bioequivalent
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products^[2,6]

In other words, both brand and generic drug entities must meet the same developmental, manufacturing, and clinical quality standards. However, generic products do not have to duplicate animal or human research data obtained in clinical trials. Since generic manufacturers are not required to provide such data, they are financially able to offer patients the same drug entity at a much lower cost. Because both brand and generic drugs must successfully complete this rigorous approval process, patients and providers can fully expect that the generic product will produce the same clinical effect and safety profile as the innovator drug.^[8,9]

Determination of Bioequivalence

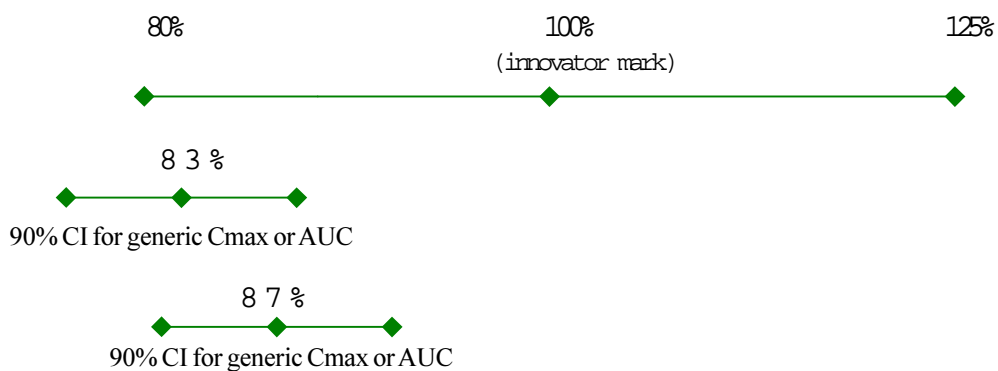
In order to be labeled therapeutically equivalent ("A"-rated) by the FDA, a drug must be both *pharmaceutically equivalent* and *bioequivalent*. A pharmaceutically equivalent generic drug has the same active ingredient, strength, dosage form and route of administration, and comparable labeling as the innovator product. A bioequivalent generic drug must demonstrate "the absence of a significant difference in the *rate* and *extent* to which the active ingredient or active moiety is absorbed from a pharmaceutically equivalent drug product

and becomes available at the site of action."^{5,6} The rate of absorption is usually expressed as area under the plasma drug concentration-time curve (AUC) and extent of absorption refers to maximum drug concentration (C_{max}).

Allowable Range of Variation for Generic Drugs

Based on FDA criteria, the 90% confidence interval for a generic product's AUC or C_{max} must lie entirely within a range of 80% to 125% of the innovator's value.⁸ Many have argued that the 80% to 125% range creates such a large variance that generic drug products could be less efficacious. Statistically, if the confidence interval (CI) of the generic's value must lie *entirely* within 80% to 125%, the lowest mark which it could have is 87% to 88%. Therefore, any generic product with a value below 87% would fail to meet FDA standards because the CI would fall below the lower limit of 80% (diagrammed below). The use of the 90% CI results in much stricter standards than many may realize.

One of the most compelling misconceptions is that FDA-approved generic drugs do not produce similar physiological responses and therapeutic outcomes. To dispel such concerns, in 1997 the FDA reviewed several previous studies to determine if non-bioequivalent medications had slipped through the cracks. No significant differences between the generic entity and the reference product were found.^[8, 10] The mean AUC difference between the generic and brand products was 3.47% and the difference in mean C_{max} was 4.29%.¹⁰ More importantly, an FDA official noted that these small differences between generic and the innovator products were no different than if one lot of the innovator product was compared to another.⁸



Substitution of Narrow Therapeutic Index (NTI) Drugs

The term “narrow therapeutic index” has been used to define a number of drugs that have a specific therapeutic range in which slight deviations could result in subtherapeutic or toxic levels. Although the FDA has never formally designated or classified any drugs as NTIs, over the years popular opinions have identified drugs such as warfarin, phenytoin, carbamazepine, digoxin, and theophylline as NTIs. The terminology used by FDA is “narrow therapeutic *ratio*”. According to federal regulations, a drug has a narrow therapeutic ratio if:

1. There is less than a 2-fold difference in median lethal dose (LD50) and effective dose (ED50) values, or
2. There is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
3. Safe and effective use of the drug requires careful titration and patient monitoring.

Much debate has occurred over the safety and appropriateness of generic substitution of NTI drugs. Many anecdotal reports of adverse events have been published in the medical literature. A recent review of several reports identified gaps in information and methodological oversights which left the author of this review unconvinced that a sound case could be made that harm actually occurred because of switching.⁴

The FDA has also addressed these concerns in two separate letters. In an April 1997 response to the National Association of Boards of Pharmacy, Dr. Roger Williams of the FDA’s Center of Drug Evaluation and Research (CDER) stated that “Because of the FDA’s strict bioequivalence criteria, we believe that drugs do not fall into discrete groups that would allow one to consider NTI drugs as being clearly different from other drugs for purposes of substitution.”⁸ Dr. Williams went on to conclude that “if one therapeutically equivalent drug is substituted for another, the physician, pharmacist, and patient have the FDA’s assurance that the physician should see the same clinical results and safety profile. Any differences that could exist should be no greater than one would expect if one lot of the innovator’s products was substituted for another.”⁸

In a subsequent letter dated January 1998 sent to health practitioners, Dr. Stuart Nightingale of the FDA stated “It is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a

determination of therapeutic equivalence by FDA for the drug products under consideration.”⁹

Innovator and Generic Drug Patent Exclusivity

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Amendments). Among other things, this act established the ANDA process, which was intended to expedite the availability of lower-priced generic versions once the patent of the innovator product has expired. As an added incentive to be the first company to file an ANDA, this act granted protection from competition from competing generic manufacturers for 180 days. In other words, the FDA will, in some cases, allow 180 days of generic exclusivity to the first marketed generic product. In 1994, the final rule implementing these provisions was published in the *Federal Register*.

Subsequently in 1997, Congress passed the FDA Modernization Act. One goal of this act was to provide incentives for pharmaceutical manufacturers to conduct much needed studies in children. This law, which provides an additional six months of exclusivity in return for conducting pediatric studies, is commonly known as the pediatric exclusivity provision. A recent report submitted to Congress stated that this provision has been “highly effective in generating pediatric studies on many drugs and in providing useful new information in product labelling.”¹²
(References available)

Patent Extensions on Upcoming Blockbuster Generics – Prilosec & Prozac

Prilosec (omeprazole-Astra Zeneca) and Prozac (fluoxetine-Eli Lilly) have consistently been 2 of the top ten drugs in the US. Because of their cost and high utilization, many payors have anticipated and welcomed the release of their generic counterparts, which were scheduled to be released in early 2001. However, Astra-Zeneca has successfully petitioned for six months pediatric patent exclusivity due to expire October 5, 2001. Recently, the company also filed four additional patents which could delay the release of the generic Prilosec until 2018. Currently, two NDA’s for generic omeprazole have received tentative approval from the FDA. The patent for Prozac was to expire in February 2001, but this product also received a six month pediatric exclusivity provision. This extension is due to expire August 2, 2001, and several generic manufacturers have received tentative approval from the FDA.

Between March 2000 to March 2001, Oklahoma Medicaid spent approximately \$1.1 million on Prozac and \$2.2 million on Prilosec. Based on historical generic pricing trend, the program could potentially save over \$1 million annually on generic substitution of these products alone.

Oklahoma Medicaid Generic Reimbursement

For most single-source (patent protected) medications, Oklahoma Medicaid reimbursement is calculated as Average Wholesale Price (AWP) minus 10.5%. For multisource (generic) drugs, the state and federal government have set upper limits of reimbursement to encourage the use of therapeutically equivalent generics. The Health Care Finance Administration has established a Federal Upper Limit (FUL) on several medications that have at least three "A-rated" generics available. The FUL list can be accessed on the internet at www.hcfa.gov/medicaid/drugs/drug10.htm.

In April 2000, the Oklahoma Health Care Authority implemented a State Maximum Allowable Cost (SMAC) program to supplement the FUL list, particularly with generic medications not yet assigned an FUL, or in some cases, to address pricing changes not yet reflected in an existing FUL. This list will soon be available at the OHCA website at www.ohca.state.ok.us/. Questions related to a SMAC value can be directed to the Oklahoma Medicaid Pharmacy Help Desk.

The FUL and SMAC values have been implemented to encourage the use of "A"-rated generic alternatives. In the unusual instance that a prescriber deems the brand name version is necessary, Oklahoma Medicaid will allow a Dispense-as-Written (DAW) override.

**Top 10 Generic Drugs (Rx volume)
Oklahoma Medicaid SFY 2000**

1. Furosemide	(103,039)
2. Potassium Chloride	(102,556)
3. Hydrocodone/APAP	(93,398)
4. Amoxicillin	(89,062)
5. Ranitidine	(81,091)
6. Propoxyphene/APAP	(51,107)
7. Cephalexin	(38,902)
8. Clonidine	(33,598)
9. Ibuprofen	(33,585)
10. SMZ/TMP	(29,929)

**Medicaid Pharmacy Help Desk
Contact Numbers**

271-6349	(Pharmacist OKC metro)
1-800-831-8921	(Pharmacist toll free)
271-9048	(Prescriber OKC metro)
1-877-269-2768	(Prescriber toll free)

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