Generic Substitution Issues for Warfarin and Levothyroxine
By Rose-Ellen Hope, R.Ph., OSU College of Pharmacy and Kathy Ketchum, B.S. Pharm., M.P.A./HA, OSU College of Pharmacy

Generic use is widely recognized to lower drug costs while preserving healthcare quality. The Oregon Health Plan (OHP) is a national leader among Medicaid programs in high generic use.

Unless brand is requested by the prescriber, Oregon pharmacy law allows the dispensing of a generic drug of the same strength, quantity, dose and dosage form as the prescribed drug that is, in the pharmacist's professional opinion, therapeutically equivalent and only when there will be a savings in or no increase in cost to the purchaser. Many managed care plans, and the OHP, use Maximum Allowable Cost (MAC) pricing to amplify the cost-avoidance from generic use.

All of this motivates pharmacies to fill prescriptions with the lowest cost generics available to them. While professionally and financially sound practice, this may result in patients frequently switching among different generic products during the course of treatment. For most drugs this does not pose harm. However, frequent switching among generic products for some drugs may be problematic, especially if prescribers and patients are unaware of such changes.

BACKGROUND
The 1984 Drug Competition and Patent Term Restoration Act, also called the Hatch-Waxman Act, expedited approval of generic drugs resulting in considerable prescription savings. Use of generics saved $8-$10 billion at retail in 1994 according to the Congressional Budget Office. Manufacturers of generics file an Abbreviated New Drug Application (ANDA) that does not require additional clinical trials. The FDA requires generics have identical active ingredient(s), strength, dosage form, method of administration, purity and stability as the innovator drug. Generics may differ in inert ingredients, such as excipients, binders, fillers, coloring agents, flavors, preservatives, release mechanisms, and scoring configuration.

In 1986, the FDA established methodology for bioequivalency testing. Establishing bioequivalence is contingent on a 90% confidence interval (CI) around the peak serum concentration (Cmax) and areas under the curve (AUC) of the generic falling within 80-125% of the reference drug in a 2-way crossover study of between 24 to 36 health volunteers. An allowable variation in content can occur among lots and even within a single lot of brand and generic drugs. The adequacy of this methodology has been questioned for so called “narrow therapeutic index” drugs such as levothyroxine and warfarin.

LEVOTHYROXINE
The American Association of Clinical Endocrinologists, The Endocrine Society, and American Thyroid Association object to the FDA relying on bioequivalency methods to establish therapeutic equivalence for levothyroxine. They cite one open-label, single-dose, study of levothyroxine in 36 healthy euthyroid volunteers. Using three doses of Synthroid, the study compared FDA bioequivalence methodology to three modifications correcting for endogenous thyroxine levels in order to determine if these could distinguish dose differences of 12.5%, 25%, or 33%. None distinguished 12.5% differences. The three methods of mathematical correction did distinguish differences of 25-33%

Before 1962, levothyroxine lacked bioequivalence data. Between 1987 and 1994, there were 47 Adverse Drug Reports (ADR) related to sub-potency, and nine to super-potency of levothyroxine. Some of these ADR were caused by switching products, but also by inconsistencies in bioavailability between lots from the same manufacturer. Bioequivalency data on levothyroxine generics are still sparse. The primary study supporting a levothyroxine generic, published in 1997, concluded that Synthroid, Levoxyl, and two other generics to be bioequivalent and interchangeable in the majority of patients.

WARFARIN
Substitution of Coumadin has also been controversial and a target of litigation. Generic warfarin, withdrawn in 1992, was reintroduced in 1997. However, product variation is but one of many possible causes for unstable INR values. Diet, drug interactions, exercise, co-morbidities, and non-compliance are just a few that contribute to varying INRs.

Seven published, clinical studies comparing Coumadin to generics were reviewed. Two evaluated generics not available in the US. One randomized, controlled, crossover, observer-blind trial is available in abstract. It enrolled 55 patients with atrial fibrillation at a VA hospital clinic, but evaluated only 39 patients who did not require warfarin dose changes or experience adverse events during the study period of 42 days.

The remaining four studies concluded therapeutic equivalence with some caveats. Milligan et al used a statistical process control to detect changes that were not random. Twelve serious adverse events occurred prior to switch and 3 after, suggesting the sample size was too small to detect rare adverse events. Witt et al had a statistical difference in the primary endpoint, “Time in target INR range,” but the clinical relevance of this difference was not borne out in number of INR tests per patient or dose changes per patient.
Weibert et al20 did not detect differences in any endpoints, but it excluded most unstable patients and cannot be generalized easily. Less than 10% of patients screened were enrolled and the focus of the study was primarily men on stable doses of warfarin being treated for atrial fibrillation. Finally, Swenson et al21 compared patients who voluntarily switched products to a comparable control and found no differences in INR control.

CONCLUSION
In a 1997 letter to the National Boards of Pharmacy the FDA stated they believed drugs do not fall into discrete groups that would allow one to consider some drugs as clearly different from other drugs for purposes of therapeutic substitution. However, the Medical Letter stated the measurement of bioequivalence is not the same as therapeutic equivalence for narrow therapeutic index (NTI) drugs and could have adverse clinical outcomes.10 According to FDA, they have received no documented examples of failure of a generic due to bioequivalence determination.

An Oregon DUR Board evaluation revealed that more than 30% of patients on levothyroxine and 18% of patients on warfarin for more than 180 days had at least one product switch.22 Outcomes for those patients were not evaluated. A recent retrospective study found half of outpatients did not receive recommended monitoring of levothyroxine.23 Generic drugs provide excellent value and their use is encouraged to help defray the rising costs of prescription drugs for the OHP. However, given the many factors that affect drug levels, product switching should be minimized for both levothyroxine and warfarin.

The DUR Board made these recommendations:
1) Stabilize patients on a single generic product. 
   a. Prescribers may want to specify this on the prescription with a note to: “Maintain on same generic product; please contact if product change made”
   b. Under fee-for-service billing rules, pharmacists may dispense 3 months in one dispensing of levothyroxine.
2) If product switching is necessary
   a. Pharmacies should substitute only AB-rated products (i.e. FDA bioequivalents): http://www.fda.gov/cder
   b. Pharmacies should notify prescribers of a switch. This provides the opportunity to monitor the patient and adjust the dose if needed.
   c. Notify and counsel patient of switch so they are aware of potential issues.


Examples of specific language on levothyroxine and warfarin for patients and sample fax notification forms for product switches, which can be used or adapted, are posted on “prescriber tools” at http://pharmacy.oregonstate.edu/drug_policy/drug_policy.html.

References:
10 Generic Levothyroxine. The Medical Letter 2004; 46 (1192): 77-78.
18 Neutel, JM, Smith DHG. A randomized crossover study to compare the efficacy and tolerability of Barr warfarin sodium to the currently available Coumadin. Cardiovas Rev Rep 1998; 19:49-59.

Reviewed by Michele Koder, PharmD and Dan Hartung, PharmD, OSU College of Pharmacy.