



Generic Substitution: Issues for Problematic Drugs

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ABSTRACT: The methodology and criteria for bioequivalence testing have been firmly established by the Food and Drug Administration (FDA). For certain drugs with a narrow therapeutic index (eg, digoxin, levothyroxine, warfarin), generic substitution may not be advisable or even allowable, depending on the substitution laws of individual states. Digoxin and levothyroxine tablets are examples of drugs for which no New Drug Applications (NDAs) currently exist. However, commercially available generic products for both of these drugs have not been determined by the FDA to be therapeutically equivalent to the innovator products. Generic versions of warfarin have been approved by the FDA as being therapeutically equivalent to the innovator products, as have generic versions of the rescue inhaler albuterol. Yet, misinformation and myths persist regarding the adequacy and proven reliability of the FDA's determination of bioequivalence for these products.

SINCE THE PASSAGE of the Drug Price Competition and Patent Term Restoration Act in 1984, commonly known as the Waxman-Hatch Act, a virtual explosion has occurred in the number of Abbreviated New Drug Applications (ANDAs) submitted to the FDA from generic drug sponsors seeking approval for generic drugs.¹ In 1980, the FDA first published a list of approved drugs, consisting of innovator drugs approved through the NDA process and the generic products considered by the FDA to be therapeutically equivalent to these innovator products. The Waxman-Hatch Act mandated that the FDA continue to publish this list of *Approved Drug Products With Therapeutic Equivalence Evaluations*, referred to as the Orange Book.² As of September 1999, a total of 9,939 approved drugs were listed, with 6,923 of these as multi-source products, including innovator products and their therapeutically equivalent generic versions. With so many generic drugs available, practitioners should be aware of some drugs for which generic substitution is either not advisable or is the subject of current controversy. In this article, we describe certain drugs and conditions in which authorization of generic substitution is either controversial or should not occur.

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BACKGROUND

Table 1 shows the system used by the FDA for rating the therapeutic equivalence of approved drugs. Drugs that are solid oral dosage forms (suspensions, capsules, tablets) and have been determined by the FDA to be therapeutically equivalent are rated "AA" or "AB." If drugs are rated to be therapeutically equivalent, then they may be generically substituted for each other with the assurance of efficacy and safety. The procedures used by the FDA for approval of generic drugs have been described and recommendations made regarding generic substitution.^{3,6} However, there are widely used and significant drugs for which the appropriateness of generic substitution should be examined. Four such drugs are described in this paper.

DIGOXIN

Digoxin in tablet form is not listed in the Orange Book, since this is a "grandfathered" dosage form of digoxin.⁷ Since the tablet formulation of digoxin was established in clinical use before passage of the Federal Food, Drug, and Cosmetic Act of 1938, generic versions of digoxin tablets may be marketed without an approved ANDA. Data showing bioequivalence of generic digoxin tablet products to the innovator product Lanoxin are generally not available or forthcoming, so that comparable rate and extent of absorption between generic products and Lanoxin brand tablets, or between different generic products, is not ensured.⁸ Seventeen generic digoxin tablets (0.25 mg) have been

TABLE 1. Therapeutic Equivalence Codes²

<i>Rating</i>	<i>Comments</i>
A	Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products because either there are no known or suspected bioequivalence problems, or bioequivalence problems have been resolved with in vivo or in vitro data confirming bioequivalence
AA	Products in conventional dosage forms not presenting bioequivalence problems
AB	Products meeting necessary bioequivalence requirements
AN	Solutions and powders for aerosolization
AO	Injectable oil solutions
AP	Injectable aqueous solutions and, in certain instances, intravenous nonaqueous solutions
B	Drug products that FDA, at present, considers not to be therapeutically equivalent to other pharmaceutically equivalent drug products
BC	Extended release dosage forms (capsules, injectables, and tablets)
BD	Active ingredients and dosage forms with documented bioequivalence problems
BE	Delayed-release oral dosage forms
BN	Products in aerosol-nebulizer drug delivery systems
BP	Active ingredients and dosage forms with potential bioequivalence problems
BR	Suppositories or enemas that deliver drugs for systemic absorption
BS	Products having drug standard deficiencies
BT	Topical products with bioequivalence issues
BX	Drug products for which data are insufficient to determine therapeutic equivalence
B	Drug products requiring further FDA investigation and review to determine therapeutic equivalence

FDA = Food and Drug Administration.

listed as currently marketed, though some of these may be marketed by suppliers or distributors of another manufacturer's product.⁹ Without pharmacokinetic data to verify the bioequivalence of these products to Lanoxin, the clinical responses (both therapeutic and toxic) from these generic products compared with Lanoxin are unpredictable. This inability to guarantee therapeutic equivalence to a reference product opposes the entire premise of generic substitution: the practitioner should expect the same responses (no more, no less) from a therapeutically equivalent generic product. Consequently, generic substitution is not advised. Use of a generic digoxin product as initial therapy may result in lower or higher than expected bioavailability, requiring additional monitoring and dosage adjustment, and ultimately increasing costs of therapy far above the cost savings from a less expensive generic product.

LEVOTHYROXINE

Levothyroxine sodium tablets are also currently not listed in the Orange Book. In the words of the FDA, "Levothyroxine sodium was

first introduced into the market before 1962 without an approved NDA, apparently in the belief that it was not a new drug."¹⁰ The lack of bioequivalence data of generic preparations to the two major brand name products Synthroid and Levothroid has been noted, along with the adoption in 1984 of *United States Pharmacopoeia (USP)* guidelines for potency of levothyroxine sodium tablets.¹¹ However, between 1987 and 1994, a total of 58 adverse drug experience reports with levothyroxine sodium tablets were received by the FDA, with 47 of the incidences apparently related to subpotency and 9 incidences related to superpotency.¹⁰ These adverse events were caused not only by switching product brands, but also by inconsistencies in bioavailability between different lots from the same source.¹⁰

Bioequivalence issues regarding levothyroxine sodium tablets were highlighted when the results of a bioequivalence study comparing the innovator product Synthroid with several generic brands finally appeared in the literature.¹² The study sponsor (the marketer of Synthroid) attempted to prevent publication of these results, which claimed bioequivalence of Synthroid to three other levothyroxine sodium products. After publication of these study results, advertisements appeared in journals and trade magazines advocating the substitution of other brand-name levothyroxine sodium products (eg, Levothroid, Levoxyl) for Synthroid. In addition, statements were made such as "Feel comfortable using Levothroid, Levoxyl, or Synthroid in hypothyroid patients. These three are bioequivalent...even though they're not AB-rated."¹³

Several points should be considered before routinely switching marketed brands of levothyroxine sodium tablets (at least 24 products for the 0.1 mg tablet are listed).⁹ First, although the conclusions stated in the peer-reviewed bioequivalence study cited appear to be generally accepted, the results of this study were not subjected to the scrutiny of the FDA review process. In view of significant stability and potency problems, the FDA has issued a Federal Register notice stating that (1) orally administered levothyroxine sodium products are now considered new drugs, and (2) manufacturers who intend to continue marketing these products must submit an NDA within 3 years to obtain approval.¹⁰ Recently, the FDA extended this deadline for an additional year.¹⁴ Second, the impression that all levothyroxine sodium tablet formulations are likely to be bio-

TABLE 2. Bioavailability Parameters for Assessment of Bioequivalence

<i>Parameter</i>	<i>Measurement</i>
Area under the curve (AUC)	Total area enclosed by the plasma concentration-time curve; measures the amount of drug reaching the systemic circulation and is directly proportional to the amount of drug absorbed
Peak concentration (C _{MAX})	Maximum drug concentration observed in the plasma; value is dependent on specific sampling times after dosing
Peak time (T _{MAX})	Time after dosing at which the maximum drug concentration is observed; value is dependent on specific sampling times

AUC is determined by collecting serial blood samples at designated times after subjects have received the drug formulation (innovator or generic). Times of collection are based on knowledge of the drug's pharmacokinetic behavior such that a sufficient number of data points are obtained that define the absorption phase (from time = 0 to time = T_{MAX}) and the elimination phase (from time = T_{MAX} to a time point representing at least 3 elimination half-lives, allowing estimation of the elimination rate constant). AUC is calculated using the "trapezoidal rule." Each pair of consecutive data points (eg, c₁, t₁ and c₂, t₂) is used to form a trapezoid from which the area is calculated with the geometric formula for a trapezoid. These areas are summed to give the total AUC, referred to as the AUC_{0-t}. An additional measurement of AUC extrapolated to infinity (AUC_{inf}) is obtained by adding the term c_{last}/k_{el} to AUC_{0-t}, where c_{last} is the last measured concentration and k_{el} is the estimated elimination rate constant. Both parameters AUC_{0-t} and AUC_{inf} are termed "model-independent" or "noncompartmental," since they are not affected by the specific pharmacokinetic model for the drug's entry and passage from the body.

equivalent is not currently supported with FDA-substantiated bioequivalence data; routine substitution of these products for refills of existing prescriptions is not advisable until FDA review is complete. Third, practitioners must always comply with the substitution laws in their individual states. If a statute mandates substitution of a therapeutically equivalent or bioequivalent product, reliance upon data reported in the scientific literature may not always guarantee these requirements will be satisfied.

WARFARIN SODIUM

Three approved generic versions of warfarin sodium tablets (seven strengths) are currently listed in the Orange Book. Before approval of these generic warfarin sodium products, several states either enacted or were considering legislation to require pharmacists to obtain prescriber and patient approval for generic substitution of drugs with a narrow therapeutic index (NTI).^{15,16} In response, the FDA issued a position statement.¹⁷ The FDA's position is clear with regard to the issue of tightening confidence intervals (CIs) and changing study designs for bioequivalence determinations of NTI drugs: "To date, we have not seen data to support such proposed changes."¹⁷ In addition, Benet has stated: "I believe that the present requirements to prove bioequivalence, at least in the United States and Canada, are already so difficult and constrained that there is no possibility, even for narrow therapeutic index drugs, that dosage forms meeting the criteria could lead to therapeutic problems."¹⁸ Benet notes that drugs approved through the NDA process with NTIs, by definition, must have low intrasubject variability. Otherwise, patients would have cycles of toxicity and lack of efficacy, and therapeutic drug monitoring would be useless.¹⁹

The low intrasubject variability associated with NTI drugs ensures that patient response to a specific drug should be consistent, and the statistical criteria required by the FDA for bioequivalence appear more than adequate for confidence in generic substitution. This is especially true in light of the notable absence of data that prove otherwise. For the most part, the arguments against generic substitution of NTI drugs appear to be based on economic considerations.

Commentaries debating the suitability of generic warfarin products have focused on the results from reports of clinical studies with generic warfarin and the content uniformity requirements for warfarin sodium tablets.^{20,21} As indicated in a letter addressing these issues, no convincing and substantiated scientific data have been published showing bioinequivalence of generic warfarin products or product failure of these products in clinical studies.²² Recently, an evidence-based medicine approach was used to compare the results reported with Coumadin and a generic warfarin product in clinical studies.²³ No significant differences were found in the international normalized ratio (INR), number of dosage changes to adjust INR in range, or number of hospitalizations or incidences of bleeding between the reference and generic warfarin products. Physicians may sometimes encounter difficulties in maintaining stabilized INR in patients anticoagulated with warfarin, since "multiple drug interactions and patient variables affect warfarin levels and create difficulty in achieving consistently therapeutic INR values."²⁴ However, factors such as diet, concurrent illnesses, interacting drugs, and noncompliance are *intersubject* variables that are unrelated to the bioequivalence issue.²⁵ For crossover studies using log-transformed data, "it is largely the

within-subject distribution of values [*intrasubject* variability] that determines the validity and efficiency of the standard parametric methods of analysis.”²⁶ For NTI drugs such as warfarin, intrasubject variability, by definition, is low and the available clinical data indicate that lack of bioequivalence does not appear to be the explanation for problems experienced during warfarin therapy.

Another article introduces the concept of “switchability,” that is, the substitution of one approved generic product for another generic product.²⁷ Bioequivalence studies submitted to the FDA through an ANDA are conducted by comparing data from the proposed generic product and a reference product. The reference product is selected by the FDA and is typically the innovator or pioneer product that was originally introduced into the market. Suppose approved generic product A differed from the reference product in at least one parameter (eg, mean area-under-the-curve [AUC] values) by +4%, and that approved generic product B differed from the reference product by -4%. The net difference of generic products A and B would then be 8%; could this magnitude of difference result in bioinequivalence and lack of equivalent therapeutic response for an NTI drug?

No data were presented from any clinical studies that could support the contention that switchability for NTI drugs is problematic. Rather, phrases such as “...with NTI drugs, small variations in bioavailability can potentially pose problems” and conceptual arguments are used to suggest the need for special bioequivalence criteria to be applied to NTI drugs.²⁷ Reference is made to the FDA’s draft guidance for population and individual bioequivalence studies, which proposes the use of reference scaling (essentially, modifying the bioequivalence criteria to account for the variability of the reference product) for NTI drugs, regardless of the intrasubject variability of the reference product.²⁸ Since NTI drugs have low intrasubject variability as discussed, this approach would likely result in narrower CI requirements. However, as noted by Benet “...tightened bioequivalence intervals [for NTI drugs] can be readily met with a reasonable number of subjects.”¹⁹

Finally, a recent report further confirms the bioequivalence of generic warfarin to the innovator product.²⁹ More than 100 subjects anticoagulated with Coumadin were switched to a generic warfarin product for 8 weeks in a

nonrandomized comparative clinical observational study. The overall conclusion was that the variability in INR in patients receiving generic warfarin was not statistically significant from that seen in the control group receiving Coumadin. These investigators identified associated factors not related to the product change in subjects whose INR varied by >1.0 from baseline. This further emphasizes the critical role of interpatient factors (physical activity, dietary vitamin K, noncompliance, drug interactions, congestive heart failure, diarrhea, alcohol consumption) affecting the anticoagulant response with warfarin.

ALBUTEROL METERED-DOSE INHALERS

Four approved generic versions of albuterol metered-dose inhalers are currently listed in the Orange Book as therapeutically equivalent (AB-rated) to the reference product Ventolin. The Proventil product is rated BN, or not therapeutically equivalent to Ventolin or the four generic products. For products administered by metered-dose inhalation and intended for local therapeutic effects, the typical pharmacokinetic methods (Table 2) for evaluating bioequivalence cannot be used. Rather, an approach based on acute pharmacodynamic response (forced expiratory volume in 1 second, FEV₁) was proposed, with asthmatic patients as subjects.⁵ The statistical criteria and appropriate CIs for bioequivalence determination are not as rigidly defined for pharmacodynamic methods as for pharmacokinetic methods. Consequently, variability in patient response may be of slightly greater concern, since albuterol metered-dose inhalers are used as “rescue inhalers” for nocturnal asthma attacks (even though they are not considered NTI drugs). However, the FDA is satisfied that these products will produce equivalent therapeutic responses.

DISCUSSION

The fundamental principles underlying the concept of bioequivalence and the process of generic substitution can be summarized as follows:

1. Generic substitution is based on the premise of therapeutic equivalence; that is, the generic product will produce the exact same clinical effects (both therapeutic and toxic) as the reference product when administered under the same conditions in the same dosage in the same patient.
2. When authorizing generic substitution, the practitioner expects therapeutic equivalence between the generic product and the reference product; there-

fore, no dosage adjustment or additional monitoring should be required (above and beyond that which would normally occur with the reference product).

3. Products that are bioequivalent will be therapeutically equivalent.
4. Bioequivalence is assessed by comparison of bioavailability parameters (Table 2).

It is apparent that the key step in this process is the determination of bioequivalence; the following discussion describes the development of the FDA's criteria for bioequivalence.

The science of bioequivalence testing originated in the early 1970s from the necessity for regulatory guidelines that could be used to declare drug products to be bioequivalent. Originally, it was believed that orally administered products (suspensions, capsules, tablets) whose average bioavailability parameters differed by less than 20% should be therapeutically equivalent. The shortcomings of this approach were immediately evident, since such a criterion would theoretically allow the parameters of generic product A to differ from the reference (innovator) product by +20%, while allowing the parameters of generic product B to differ from the reference product by -20%. The net difference between the two generic products A and B would then be as much as 40% and, therefore, beyond the limits of therapeutic equivalence as originally conceived. To correct for this deficiency, the FDA adopted the "power" approach in the early 1980s. This method tested the null hypothesis (H_0) that the generic and reference products were identical, and it evaluated the power of the bioequivalence study to detect a 20% difference between the means of the parameters. If the differences between the mean values of parameters for the two products were not statistically significant ($P > .05$), and the study power was at least 80%, the products were declared bioequivalent.

However, the power approach had a major flaw because it tested the assumption of identical performance from products that were already known not to be identical. Clearly, the formulations of the reference and generic products are not identical, and differences in the extent and rate of gastrointestinal absorption are expected to occur. Therefore, it was concluded that the statistical test of no difference between the products was not the proper bioequivalence assessment. In 1986, the FDA adopted the currently used decision rule, which tests the more relevant alternative hypothesis

(H_1). This approach asks: (1) how great are the differences between the generic and reference products? and (2) more specifically, are these differences within limits that would still guarantee bioequivalence and therefore therapeutic equivalence? The determination of bioequivalence using this approach is termed "average bioequivalence."³⁰

The statistical method for the average bioequivalence assessment is termed the "two 1-sided tests" procedure. Typically, the data from a single-dose, 2-way crossover bioavailability study are analyzed using a complex statistical model that allows evaluation of the least squares means of the bioavailability parameters and their standard errors. These results are then used to construct the 90% CI for the differences in parameter means. A 90% CI is used, since a 5% statistical error is allowed at both the upper and the lower limits; therefore, the total error is 10%, generating the 90% CI. When the current rule was adopted in 1986, if both the upper and lower limits of the CI were within 20% of the reference mean (80% to 120%), the generic product was declared bioequivalent to the reference product. In 1992, the FDA issued a guidance in which the use of log-transformed data and an upper limit of 125% were adopted. These criteria remain the current rule for bioequivalence decisions.²⁶

A recent article underscores the misinformation that persists regarding the FDA criteria for generic drug approval. The article states: "Only 17% of 396 physicians were aware that FDA allows the rate and extent of absorption of a generic drug product to depart from those of the brand-name version by up to 25%. . ."³¹ "The determination of average bioequivalence is made by calculating the 90% confidence interval (CI) for the difference between generic and reference products and by requiring that the entire CI lie completely within the lower and upper limits which define bioequivalence. Currently, these limits are 80-125% of the reference product mean value using data after logarithmic transformation."⁶ Using these statistical criteria, it is difficult for any generic product whose mean arithmetic bioavailability parameters differ by more than 10% from the reference to meet the CI requirements, and it is virtually impossible to meet the CI requirements if the differences approach 20%. "A generic product that truly differs by -20%/+25% or more from the innovator product with respect to one or more pharmacoki-

netic parameters would actually have less than a 5% chance of being approved.³² An FDA study showed that the mean difference for AUC values between test and reference products was 3.5% in the 2-year period following the Waxman-Hatch Act, and that 80% of the absolute differences between generic products approved since 1984 and the corresponding innovator products were within 5%.³²

CONCLUSION

The FDA has issued a statement to medical organizations and state boards of pharmacy in response to certain groups who have raised the issue of generic substitution of NTI products.¹⁷ Two of the most important points are that (1) to date, there are no documented examples of failure of a generic drug due to bioequivalence determination; and (2) products declared as bioequivalent should not require any additional clinical testing or monitoring. For the three NTI drugs discussed, we support the substitution of AB-rated generic versions of warfarin sodium tablets, recommend against generic substitution for Lanoxin brand tablets, and advise caution against generic substitution of levothyroxine sodium tablets until the FDA declares these products to be AB-rated to the corresponding reference products. Finally, we recommend substitution of AB-rated generic versions of albuterol metered-dose inhalers.

On August 22, 2000, the FDA approved the first NDA for an oral levothyroxine sodium product, Unithroid (Jerome Stevens Pharmaceuticals, Bohemia, NY).

References

1. Pub L No. 98-417, 98 Stat 1585-1605; 21 USC 355
2. US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Management: *Approved Drug Products With Therapeutic Equivalence Evaluations*. Washington, DC, US Government Printing Office, 19th Ed, 1999
3. Henderson JD: Bioequivalence and bioavailability. *Regul Affairs* 1993; 5:367-374
4. Henderson JD: Current issues in bioequivalence determination. *Appl Clin Trials* 1992; 1:44-49
5. Henderson JD: Current issues in bioequivalence determination: Part II. *Appl Clin Trials* 1992; 1:58-61
6. Henderson JD, White GL Jr: A generic drug primer: regulatory aspects and scientific concepts. *Mil Med* 1998; 163:193-197
7. Lewis BP Jr, Castle RV Jr: Grandfathered drugs of 1938. *Am Pharm* 1978; 18:36-39

8. Kradjan WA: Congestive heart failure. *Applied Therapeutics: The Clinical Use of Drugs*. Young LY, Koda-Kimble MA (eds). Vancouver, Wash, Applied Therapeutics Inc, 6th Ed, 1995, pp 15-17
9. *Drug Topics Red Book*. Montvale, NJ, Medical Economics Co Inc, 1998, pp 275-276, 383-385, 548
10. 62 *Federal Register* 157 (1997)
11. Dong BJ: Thyroid disorders. *Applied Therapeutics: The Clinical Use of Drugs*. Young LY, Koda-Kimble MA (eds). Vancouver, Wash, Applied Therapeutics Inc, 6th Ed, 1995, pp 47-49
12. Dong BJ, Hauck WW, Gambertoglio JG, et al: Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997; 277:1205-1213
13. *Pharmacists Letter* 1997; 13:25
14. 65 *Federal Register* 24488-24489 (2000)
15. *Rx Ipsa Loquitor* 1997 (September); 24:1
16. *ASHP Newsletter* 1998 (March); 31:1
17. FDA position on product selection for "narrow therapeutic index" drugs. *Am J Health Syst Pharm* 1997; 54:1630-1632
18. Benet LZ: Narrow therapeutic index drugs. International Open Conference on Dissolution, Bioavailability, and Bioequivalence. Toronto, Canada, June 15-18, 1992, pp 35-39
19. Benet LZ, Goyan JE: Bioequivalence and narrow therapeutic index drugs. *Pharmacotherapy* 1995; 15:433-440
20. Benson SR, Vance-Bryan K: In favor of Coumadin over generic warfarin. *Am J Health Syst Pharm* 1998; 55:727-729
21. Haines ST: Reflections on generic warfarin. *Am J Health Syst Pharm* 1998; 55:729-733
22. Hopefl A: Differences in warfarin products are not the issue. *Am J Health Syst Pharm* 1998; 55:1935
23. Noviasky JA: Evidence-based pharmacy versus opinion on generic product selection of warfarin. *Am J Health Syst Pharm* 1999; 56:2246-2247
24. Malik AK, Taylor AJ: Can warfarin randomized trials be reproduced in 'real life'? adherence to warfarin guidelines for intensity of anticoagulation in a university-based warfarin clinic. *South Med J* 2000; 93:58-61
25. Hylek EM, Helman H, Skates SJ, et al: Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; 279:657-662
26. Division of Bioequivalence, Office of Generic Drugs, Food and Drug Administration: *Guidance on Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design*. Rockville, Md, Office of Training and Communications, Division of Communications Management, Drug Information Branch, 1992
27. Banahan BF III, Bonnarens JK, Bentley JP: Generic substitution of NTI drugs: issues for formulary committee consideration. *Formulary* 1998; 33:1082-1096
28. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research: *Guidance for Industry. Average, Population, and Individual Approaches to Establishing Bioequivalence (Draft Guidance)*. Rockville, Md, Office of Training and Communications, Division of Communications Management, Drug Information Branch, 1999
29. Swenson CN, Fundak G: Observational cohort study of switching warfarin sodium products in a managed care organization. *Am J Health Syst Pharm* 2000; 57:452-455
30. Schuirmann DJ: A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinetic Biopharm* 1987; 15:657-680
31. Banahan BF III, Kolassa EM: A physician survey on generic drugs and substitution of critical dose medications. *Arch Intern Med* 1997; 157:2080-2088
32. Nightingale SL, Morrison JC: Generic drugs and the prescribing physician. *JAMA* 1987; 258:1200-1204