

REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-07)
Generic Substitution of Narrow Therapeutic Index Drugs
(Resolution 527, A-06)
(Reference Committee E)

EXECUTIVE SUMMARY

Objective: To review the evidence and the arguments surrounding the generic substitution of narrow therapeutic index (NTI) drugs.

Methods: Previous reports of this Council on generic drugs were reviewed. Published studies from 2002 through February 2007 were identified through a MEDLINE search of English-language articles, using the MeSH terms, “drugs, generic,” and “therapeutic equivalency.” A total of 103 articles were identified. Additional articles were identified by a review of references cited in these publications. In addition, the Web sites of the Food and Drug Administration (FDA) and various medical specialty societies were accessed for articles relevant to NTI drugs.

Results: Generic drugs are significantly less expensive than brand name innovator drugs and provide an opportunity to reduce spending on pharmaceuticals in the United States. The FDA considers generic drug products to be “therapeutically equivalent” to brand name innovator products if they are pharmaceutical equivalents and show bioequivalence in healthy volunteers; such products receive an “A-rating.” The FDA applies the same approval criteria for NTI drugs, which the Agency calls “narrow therapeutic range” drugs. Some physicians remain concerned about generic substitution of NTI drugs because of small differences between therapeutic and toxic doses and the need for therapeutic drug concentration or pharmacodynamic monitoring. However, scientific evidence to support these concerns either does not exist or is extremely weak. In large part, studies reviewed and cited in this report suggest “AB-rated” generic NTI drugs were bioequivalent to their brand name innovator products in patients with diseases for which the drugs are indicated.

Conclusion: Consistent with current American Medical Association (AMA) Policy H-125.984(1) (AMA Policy Database), the prescribing physician should ultimately make the decision on whether to allow generic substitution of an NTI drug for an individual patient. Furthermore, as stated in current AMA Policy H-115.994(4), when a prescription for a generic drug product is refilled (e.g., for a patient with a chronic disease), changing the manufacturer should be discouraged, whenever possible, to avoid confusion for the patient. For many drugs, especially those with a narrow therapeutic range, therapeutic drug concentration or pharmacodynamic monitoring is necessary to assure the desired clinical response. Such monitoring is necessary irrespective of whether the drug is a brand name or generic product. In addition, patients must receive adequate education to be able to fully understand the nature and proper use of their medications.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-A-07

Subject: Generic Substitution of Narrow Therapeutic Index Drugs
(Resolution 527, A-06)

Presented by: Mohamed K. Khan, MD, PhD, Chair

Referred to: Reference Committee E
(Paul C. Matson, MD, Chair)

1 Resolution 527, introduced by the Georgia Delegation at the 2006 Annual Meeting and referred
2 to the Board of Trustees, asks:

3
4 That our American Medical Association (AMA) adopt a policy in support of the
5 Centers for Medicare and Medicaid Services prohibiting any substitutions of a
6 prescribed medication with a narrow therapeutic index with another
7 manufacturer's form of the same medication with a narrow therapeutic index on a
8 Medicare Part D Prescription Plan chosen by the patient, without first submitting
9 written notification of such change by the formulary to the patient and the
10 prescribing physician; and

11
12 That our AMA request the Centers for Medicare and Medicaid Services produce
13 guidelines prohibiting any substitution of physician prescribed medications with
14 a narrow therapeutic index, as defined using the [Food and Drug Administration]
15 requirements, from a certain manufacturer to any other manufacturer's form of
16 that medication on a Medicare Part D Prescription Plan, without first submitting
17 written notification of such change by the formulary to the patient and the
18 prescribing physician.

19
20 At the 2002 Annual Meeting, this Council presented a report on generic drugs, which included a
21 detailed discussion of the generic substitution of narrow therapeutic index (NTI) drugs.¹ The
22 following report will provide an update of the earlier report with a focus on the evidence and the
23 arguments surrounding the generic substitution of NTI drugs.

24
25 Methods

26
27 Previous reports of this Council on generic drugs were reviewed. Published studies from 2002
28 through February 2007 were identified through a MEDLINE search of English-language articles,
29 using the MeSH terms, "drugs, generic," and "therapeutic equivalency." A total of 103 articles
30 were identified. Additional articles were identified by a review of references cited in these
31 publications. In addition, the Web sites of the Food and Drug Administration (FDA) and various
32 medical specialty societies were accessed for articles relevant to NTI drugs.

1 AMA Policies

2
3 AMA Policy H-125.984 (AMA Policy Database) is our AMA's primary policy on generic drugs,
4 as follows:

5
6 "Our AMA believes that: (1) Physicians should be free to use either the generic or brand name in
7 prescribing drugs for their patients, and physicians should supplement medical judgments with
8 cost considerations in making this choice. (2) It should be recognized that generic drugs
9 frequently can be less costly alternatives to brand-name products. (3) Substitution with Food and
10 Drug Administration (FDA) "B"-rated generic drug products (i.e., products with potential or
11 known bioequivalence problems) should be prohibited by law, except when there is prior
12 authorization from the prescribing physician. (4) Physicians should report serious adverse events
13 that may be related to generic substitution, including the name, dosage form, and the
14 manufacturer, to the FDA's MedWatch program. (5) The FDA, in conjunction with our AMA
15 and the United States Pharmacopoeia, should explore ways to more effectively inform physicians
16 about the bioequivalence of generic drugs, including decisional criteria used to determine the
17 bioequivalence of individual products. (6) The FDA should fund or conduct additional research
18 in order to identify the optimum methodology to determine bioequivalence, including the concept
19 of individual bioequivalence, between pharmaceutically equivalent drug products (i.e., products
20 that contain the same active ingredient(s), are of the same dosage form, route of administration,
21 and are identical in strength). (7) The Congress should provide adequate resources to the FDA to
22 continue to support an effective generic drug approval process. (CSA Rep. 6, A-02)"

23
24 AMA Policy H-115.974 also is relevant to generic substitution and the dispensing of generic drug
25 products, as follows:

26
27 "Our AMA recommends (1) That when a physician desires to prescribe a brand name drug
28 product, he or she do so by designating the brand name drug product and the phrase "Do Not
29 Substitute" (or comparable phrase or designation, as required by state law or regulation) on the
30 prescription; and when a physician desires to prescribe a generic drug product, he or she do so by
31 designating the USAN-assigned generic name of the drug on the prescription. (2) That, except
32 where the prescribing physician has indicated otherwise, the pharmacist should include the
33 following information on the label affixed to the container in which a prescription drug is
34 dispensed: in the absence of product substitution, (a) the brand and generic name of the drug
35 dispensed; (b) the strength, if more than one strength of drug is marketed; (c) the quantity
36 dispensed; and (d) the name of the manufacturer or distributor. (3) When generic substitution
37 occurs: (a) the generic name (or, when applicable, the brand name of the generic substitute
38 ["branded" generic name]) of the drug dispensed; (b) the strength, if more than one strength of
39 drug is marketed; (c) the quantity dispensed; (d) the manufacturer or distributor; and (e) either the
40 phrase "generic for [brand name prescribed]" or the phrase "substituted for [brand name
41 prescribed]". (4) When a prescription for a generic drug product is refilled (e.g., for a patient
42 with a chronic disease), changing the manufacturer or distributor should be discouraged to avoid
43 confusion for the patient; when this is not possible, the dispensing pharmacist should satisfy the
44 following conditions: (a) orally explain to the patient that the generic drug product being
45 dispensed is from a different manufacturer or distributor and, if possible (e.g., for solid oral
46 dosage forms), visually show the product being dispensed to the patient; (b) replace the name of
47 the prior generic drug manufacturer or distributor on the label affixed to the prescription drug
48 container with the name of the new generic drug manufacturer or distributor and, show this to the
49 patient; (c) affix to the primary label an auxiliary (sticker) label that states, "This is the same
50 medication you have been getting. Color, size, or shape may appear different"; and (d) place a
51 notation on the prescription record that contains the name of the new generic drug manufacturer

1 or distributor and the date the product was dispensed. (BOT Rep. 1, A-95; Amended: CSA Rep.
2 2, I-99; Modified Res. 512, I-00; Reaffirmed: CSA Rep. 6, A-02)”

3 4 Generic Drug Use and Costs

5
6 Generic drugs accounted for 56% of all prescriptions dispensed in the United States in 2005, but
7 this represented less than 13% of every dollar spent on prescription drugs. The average retail
8 price of a prescription for a generic drug was \$29.82 versus \$101.71 for a brand name drug.²
9 Thus, the use of generic drugs provides an opportunity to substantially reduce spending on
10 pharmaceuticals. For this reason, the Medicare Part D outpatient prescription drug program
11 strongly encourages the use of generic drugs whenever possible, and the Centers for Medicare
12 and Medicaid Services (CMS) reported that 61% of Part D prescriptions dispensed in the third
13 quarter of 2006 were for generic drugs.³

14 15 Approval of Generic Drug Products

16
17 CSA Report 6 (A-02) provided an extensive discussion of this subject,¹ and the following is a
18 synopsis of that discussion to provide context for the current report. Generic drug products are
19 approved in the United States via the Abbreviated New Drug Application (ANDA) process.
20 Generic products approved under an ANDA must be “pharmaceutical equivalents” (i.e., have the
21 same active ingredient[s], route of administration, dosage form, and strength) of the reference
22 drug (brand name innovator) product. They must also be “bioequivalent” and the manufacturer
23 must supply other basic technical information related to manufacturing of the product that is
24 normally required of any New Drug Application (NDA).^{1,4}

25
26 Bioequivalence is defined as “the absence of a significant difference in the rate and extent to
27 which the active ingredient or active moiety in pharmaceutical equivalents...becomes available at
28 the site of drug action when administered at the same molar dose under similar conditions in an
29 appropriately designed study.”^{4,5} The FDA currently uses an “average bioequivalence” approach,
30 which involves a comparison of means. For immediate-release oral dosage forms, the standard
31 average bioequivalence determination employs a single-dose, two-way crossover study, typically
32 conducted in a limited number of healthy volunteers (usually 24 to 36 adults). For drugs with
33 long half-lives, parallel design studies may be used. Both the rate and extent of absorption are
34 evaluated. The former includes the maximum plasma concentration (C_{max}) and the time required
35 to achieve this value (T_{max}). The extent of absorption is measured by the area under the plasma
36 concentration-time curve (AUC). Results are analyzed according to whether the generic product
37 (test), when substituted for the brand name product (reference), is significantly less bioavailable,
38 and alternatively, whether the brand name product, when substituted for a generic product, is
39 significantly less bioavailable (the two 1-sided tests). The core of the bioequivalence concept is
40 an “absence of a significant difference.” A difference of >20% is viewed by the FDA as
41 significant. By convention, all data are expressed as a ratio of the average response (AUC and
42 C_{max}) for test/reference, so the limit expressed in the second analysis is 125% (reciprocal of 80%).
43 Tests are carried out using an analysis of variance and calculating a 90% confidence interval (CI)
44 for the average of each pharmacokinetic parameter, which must be entirely within the 80% to
45 125% boundaries.^{1,4,5}

46
47 The FDA considers generic drug products to be “therapeutically equivalent” to brand name
48 innovator products if they meet the criteria outlined above, even though other characteristics of
49 the product (e.g., shape, color, excipients) may be different. Generic drug products that the FDA
50 considers to be therapeutically equivalent to brand name innovator products are “A-rated,” and
51 those that are not therapeutically equivalent are “B-rated.” These are the first letters of

1 therapeutic equivalence evaluation codes for all drug products listed in the FDA's publication,
2 *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).⁴ A second
3 letter follows the "A" or "B" rating and provides additional information on the basis for the
4 FDA's evaluation. For example, most orally administered generic drug products that are
5 therapeutically equivalent are designated with the code "AB," which means that actual or
6 potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro
7 evidence supporting bioequivalence.⁴

8
9 Concerns have been raised as to whether assessment of bioequivalence assures therapeutic
10 equivalence, and numerous case reports have appeared in the medical literature suggesting
11 problems temporally related to generic substitutions with a number of "A-rated" products.¹
12 However, the FDA has investigated numerous reports of potential generic product inequivalence,
13 and the Agency has claimed it cannot document a single example of therapeutic failure when an
14 FDA-designated therapeutically equivalent product was substituted for its reference (brand name
15 innovator) product.^{1,6} The FDA also has conducted two large surveys to quantify the differences
16 between generic and brand name products. The first, conducted on 224 bioequivalence studies
17 submitted in approved applications during 1985 and 1986, found an average difference in AUC
18 measures between reference and generic products of 3.5%.⁷ The second, involving 127
19 bioequivalence studies submitted in 1997 found average differences of 3.47% for AUC and
20 4.29% for C_{max} .⁸ Finally, it is important to emphasize that when the formulation of a brand name
21 innovator drug product is changed by its manufacturer, not an infrequent occurrence, the identical
22 bioequivalence tests are performed to show therapeutic equivalence.¹

23 24 Generic Substitution of Narrow Therapeutic Index Drugs

25
26 Therapeutic Equivalence Considerations. There is no universally accepted definition of an NTI
27 drug. The FDA prefers to use the term "narrow therapeutic range," but notes that "narrow
28 therapeutic index" is more commonly used. In its most recent *Guidance for Industry:*
29 *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General*
30 *Considerations*, the FDA defines narrow therapeutic range drug products "as containing certain
31 drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring,
32 and/or where product labeling indicates a narrow therapeutic range designation." Examples cited
33 by the FDA include: digoxin, lithium, phenytoin, theophylline, and warfarin. While the FDA
34 Guidance recommends that sponsors (manufacturers) consider additional testing and/or controls
35 to ensure the quality of narrow therapeutic range drug products, the Guidance recommends that
36 "the traditional bioequivalence limit of 80 and 125 percent for non-narrow therapeutic range
37 drugs remain unchanged for the bioavailability measures (AUC and C_{max}) of narrow therapeutic
38 range drugs."⁵

39
40 As discussed in CSA Report 6 (A-02), surveys and guidelines confirm that some physicians
41 remain concerned about the potential therapeutic inequivalence of generic NTI products,
42 including antiepileptic drugs, antiarrhythmics, warfarin, and cyclosporine.¹ These include current
43 position statements of the: 1) American Academy of Neurology that: a) opposes generic
44 substitution of anticonvulsant drugs for the treatment of epilepsy without the attending
45 physician's approval; and b) opposes prior authorization requirements by public and private
46 formularies for anticonvulsant drugs in the treatment of epilepsy⁹; and 2) American Association
47 of Clinical Endocrinologists, The Endocrine Society, and the American Thyroid Association
48 (joint statement) that: a) raises concerns with the FDA's method for determining bioequivalence
49 for generic levothyroxine products; and b) recommends that physicians not substitute
50 levothyroxine drug products.¹⁰ Our AMA also has a policy directive (D-125.991) that urges the
51 FDA to re-examine its bioequivalence standards for levothyroxine.

1 CSA Report 6 (A-02) contained a detailed discussion of both the evidence and the arguments
2 surrounding the generic substitution of NTI drugs, including antiepileptic drugs, antiarrhythmic
3 drugs, warfarin, and cyclosporine.¹ The current report briefly reviews the more recent (since
4 2002), but limited published studies that were conducted in the United States.

5
6 *Antiepileptic Drugs.* Based on a retrospective review of approximately 200 medical records of
7 patients with seizures who had been mandated to switch from Dilantin Kapseals to an “AB-rated”
8 generic phenytoin product (Mylan Pharmaceuticals) in State of Minnesota health plans without
9 physician notification, eight adult patients were identified whose seizures increased such that they
10 were switched back to the brand name product. Mean total phenytoin serum concentration on
11 brand was 17.7 ± 5.3 mg/L, decreased to 12.5 ± 2.7 mg/L on generic, and increased to 17.8 ± 3.9
12 mg/L after brand was re-introduced. Unbound phenytoin serum concentrations decreased in each
13 of the eight patients when switched to generic. This small observational study had obvious
14 limitations, however.¹¹

15
16 *Antiarrhythmic Drugs.* A retrospective chart review was performed on 138 patients with cardiac
17 arrhythmias in a Veterans Administration (VA) Medical Center who were taking a stable dose of
18 amiodarone before and after switching from Cordarone, the brand name innovator product, to an
19 “AB-rated” generic product (Pacerone from Upsher-Smith Laboratories). For 77 patients who
20 took each product at the same dose, steady-state plasma concentrations of amiodarone and its
21 active metabolite, desethylamiodarone (DEA), did not differ among the two drug products.
22 However, after substitution with the generic product, 11 patients experienced a large change of
23 $\geq 100\%$ in amiodarone concentrations. Because of limitations in the study design, it could not be
24 definitively concluded that these changes were due to the change in drug formulation. Plasma
25 concentrations of the active metabolite DEA were very stable after the switch, and no patient
26 developed new clinical evidence of toxicity. The authors concluded that it is possible to switch
27 amiodarone products with minimal risk to the vast majority of patients. Monitoring of drug
28 concentrations in plasma is warranted.¹²

29
30 *Warfarin.* An anticoagulation clinic associated with an HMO collected data on 182 patients
31 eight months prior to and 10 months after the substitution of an “AB-rated” generic warfarin
32 product (Barr Laboratories) for Coumadin (brand name innovator product) for the following
33 endpoints: 1) international normalized ratio (INR) control; 2) frequency of INR monitoring; 3)
34 number of dose changes; and 4) rate of thrombotic and hemorrhagic events. No differences were
35 found in any endpoint. The authors concluded that generic substitution of warfarin could be done
36 safely without the need for additional monitoring.¹³

37
38 A nonprofit, group model HMO began a system-wide conversion of patients from Coumadin to
39 an “AB-rated” generic warfarin product (Barr Laboratories). A retrospective study was done on
40 2,299 patients who had been taking warfarin for at least 180 days and who had received
41 uninterrupted oral anticoagulation therapy during the 90 days before and 90 days after switching
42 to generic warfarin. The primary endpoint was the calculated amount of time each patient’s INR
43 values were within the patient-specific target INR range in the 90 days before and after the
44 switch. Data also were collected on adverse events and medical resource utilization, and a
45 pharmaco-economic analysis was performed. The overall difference in calculated time INR
46 values was below (22.6% before vs. 26.1% after switch, $p=0.0001$) and within (65.9% before vs.
47 63.3% after switch, $p=0.0002$) the therapeutic INR range was statistically but not clinically
48 significant. Only 28% of patients experienced a change in therapeutic INR control of 10% or
49 less, 33.1% experienced INR control that improved by greater than 10%, and 38.9% experienced
50 INR control that worsened by more than 10%. The INR control varied by greater than 50% after
51 product conversion in 13% of patients. Whether this variability in anticoagulation response was

1 directly attributable to generic substitution or simply reflects the inherent variability associated
2 with warfarin therapy could not be determined. No statistically significant difference was noted
3 in the number of nonfatal anticoagulation-related adverse events after generic substitution, and
4 the proportion of patients who actually experienced adverse events was small. However, the
5 study design prevented analysis of adverse events that necessitated withdrawal of patients from
6 the study. The difference in total treatment costs associated with brand name and generic
7 warfarin was \$3,128/100 person-years in favor of the generic product. The authors concluded
8 that most patients were successfully switched from brand name to generic warfarin. The authors
9 also recommended that additional INR monitoring should occur in the days and weeks after
10 generic substitution of warfarin products.¹⁴

11
12 *Cyclosporine.* An open-label, three-period design, multicenter study was performed in 50 renal
13 transplant recipients taking stable doses of Neoral, the brand name innovator cyclosporine
14 product. Patients continued on their Neoral regimen during period I (days 1-14), switched to the
15 same dosage of an “AB-rated” generic cyclosporine product (Gengraf from Abbott Laboratories)
16 during period II (days 15-28), and switched back to the same dosage of Neoral during period III
17 (days 29-35). Twelve-hour pharmacokinetic evaluations (maximum observed blood
18 concentration [C_{max}], concentration before dosing [C_{trough}], time to maximum observed
19 concentration [T_{max}], and area under the blood concentration-vs.-time curve [AUC]) occurred on
20 days 1, 14, 15, 28, and 29. Predose C_{trough} samples also were evaluated on days 7, 21, and 35;
21 laboratory and safety parameters also were evaluated. The pharmacokinetics of the generic drug
22 product (C_{max} , T_{max} , C_{trough} , and AUC) were indistinguishable from the Neoral values in these
23 stable renal transplant patients, and the bioequivalent capsules were interchangeable with respect
24 to C_{max} , C_{trough} , and AUC at steady state and also on conversion from one capsule formulation to
25 another. The 90% confidence intervals for the generic vs. Neoral comparison at steady state (day
26 28 vs. day 14) were 0.95 to 1.03 for AUC and 0.92 to 1.04 for C_{max} . Trough concentrations
27 remained consistent throughout the study with no need for dosage adjustment in any patient, and
28 no differences in adverse events were observed. The authors concluded that the “AB-rated”
29 generic drug product was interchangeable with Neoral in stable renal transplant patients.¹⁵

30
31 Forty-one patients receiving follow-up care at a renal transplant clinic in the VA healthcare
32 system were switched from Neoral to an “AB-rated” generic cyclosporine product (Gengraf from
33 Abbott Laboratories) based on a 1:1 dosing equivalency. Steady state cyclosporine trough
34 concentrations were obtained both prior to and following the generic substitution. Patients also
35 were monitored for changes in serum creatinine, hospitalization, cyclosporine toxicity, graft
36 rejection, and need for further adjustment in cyclosporine regimen. No differences in
37 cyclosporine trough concentrations or serum creatinine were observed following the Neoral to
38 generic conversion. There were no reports of cyclosporine toxicity, no episodes of graft
39 rejection, and no need for further dosage adjustment related to generic substitution. The authors
40 concluded that the “AB-rated” generic drug product was interchangeable with Neoral in these
41 renal transplant patients.¹⁶

42
43 Among 82 stable renal transplant patients being treated with Neoral on the renal transplant unit of
44 a county medical center, 73 patients were switched to an “AB-rated” generic cyclosporine
45 product (Gengraf from Abbott Laboratories) based on a 1:1 dosing equivalency. Nine patients
46 remained on Neoral. Cyclosporine trough concentrations and serum creatinine concentrations
47 were measured prior to and at two and four weeks following the generic substitution. Thirteen of
48 73 patients who switched to the generic drug required a dosage adjustment after the mean
49 cyclosporine trough concentrations changed from 234 ± 96 ng/ml at baseline to 289 ± 102 ng/ml
50 at two weeks. None of nine patients who remained on Neoral required a dosage adjustment. No
51 significant differences in serum creatinine concentrations were observed in either group of

1 patients. The authors recommended additional drug monitoring when there is generic substitution
2 of cyclosporine.¹⁷

3
4 Clinical outcomes were compared for de novo kidney transplant recipients who received either
5 Neoral (n=100) or an “AB-rated” generic cyclosporine product (Gengraf from Abbott
6 Laboratories) (n=88) in a single-center, retrospective review. When compared to patients who
7 received Neoral, patients who received the generic cyclosporine product were significantly more
8 likely to have an acute rejection episode (39% vs. 25%, p=0.04), more likely to have a second
9 rejection episode (13% vs. 4%, p=0.03), or to have received an antibody preparation to treat acute
10 rejection (19% vs. 8%, p=0.02). Patients treated with the generic drug had a higher degree of
11 inpatient variability for cyclosporine trough concentrations as determined by % coefficient of
12 variation (%CV) (p<0.05). The authors concluded that the incidence of acute rejection post-
13 transplant was significantly higher in patients who received the generic drug when compared to
14 Neoral, and they recommended that a larger, prospective controlled clinical trial be conducted to
15 confirm their findings.¹⁸

16
17 *Levothyroxine.* No published studies on the generic substitution of levothyroxine in patients with
18 hypothyroidism were found in the CSAPH’s search of the literature since 2002.

19
20 A potential concern regarding generic substitution of levothyroxine sodium is that there are four
21 reference (brand name innovator) products, Unithroid, Synthroid, Levoxyl, and Levothroid, and
22 three-character codes, AB1, AB2, AB3, and AB4, respectively, are assigned to each of these
23 products in the FDA’s Orange Book. Generic drug products may be determined by the FDA to
24 be therapeutically equivalent to one or more of these reference products, and the reference
25 products, themselves, may be bioequivalent to one another. For example, Synthroid (AB1, AB2)
26 is considered to be therapeutically equivalent to Unithroid, but not to Levoxyl and Levothroid.
27 Generic levothyroxine sodium made by GenPharm (AB2, AB3) is considered to be
28 therapeutically equivalent to Synthroid and Levoxyl, but not to Unithroid or Levothroid. On the
29 other hand, generic levothyroxine sodium made by Mylan (AB1, AB2, AB3, AB4) is considered
30 to be therapeutically equivalent to all four reference products, even though some reference
31 products are not considered to be therapeutically equivalent to each other. Listings of
32 levothyroxine sodium products consume 20 pages of the FDA’s Orange Book.⁴ This has the
33 potential to result in considerable confusion regarding appropriate generic substitution among
34 these products in the outpatient practice environment.¹⁰

35
36 Other Patient Safety Considerations. The frequency of medication errors and preventable
37 medication-related injuries represents a very serious cause for concern. Medication errors can
38 occur at any point in the medication use process and in any care setting.¹⁹ While the focus
39 usually has been on errors caused by healthcare professionals, there is substantial evidence that
40 patient errors also are important, whether they are due to non-adherence (non-compliance) with
41 medication regimens,²⁰ inappropriate use of medications,²¹ or an inability to understand simple
42 information, such as prescription drug labels.²²

43
44 In a report of this Council entitled, “Labeling of Prescription Drug Containers for Generic-
45 Substituted Drugs” (CSA Report 2, I-99), it was recognized that the potential also exists for
46 patient confusion when a generic drug is substituted for a brand name drug, or when a pharmacist
47 changes the manufacturer of the generic drug during a refill. For example, the drug names (brand
48 vs. generic) and/or the color, shape, and markings of solid oral dosage forms may be different.²³
49 AMA Policy H-115.974 (see above) has two recommendations that are intended to minimize this
50 problem. State generic substitution laws allow physicians to designate “Do Not Substitute” (or a
51 comparable phrase or designation) on a prescription, thus allowing the physician to decide if a

1 generic drug product can be substituted. AMA Policy H-115.974(1) recommends that physicians
2 exercise this authority and clearly designate their preference when prescribing multisource drugs
3 where alternative generic products are available. AMA Policy H-115.974(4) also discourages
4 pharmacies from changing generic manufacturers when any generic prescription is refilled, and it
5 lays out recommendations for pharmacists to educate patients if this cannot be avoided. Because
6 of the potential for a disastrous outcome if there is a problem with the generic substitution of an
7 NTI drug, these recommendations are especially applicable.

8 9 Conclusion

10
11 Generic drugs are significantly less expensive than brand name innovator drugs and provide an
12 opportunity to reduce spending on pharmaceuticals in the United States. While physicians should
13 be free to use either the generic or brand name in prescribing drugs for their patients, physicians
14 should supplement medical judgments with cost considerations in making this choice (AMA
15 Policy H-125.984).

16
17 As previously discussed in CSA Report 6 (A-02), the criteria used by the FDA to ensure
18 bioequivalence among multisource drug products are widely misunderstood. These criteria do
19 not allow for -20% to +25% difference in bioavailability between products. Rather, these
20 parameters represent the statistical universe in which measures of variance must reside. In
21 practice, the mean differences in pharmacokinetic parameters for most orally administered
22 generic drug products are closer to 3% or 4%.^{1,7,8}

23
24 The FDA is confident that its methodology for approving generic drugs, including NTI drugs, is
25 adequate to establish therapeutic equivalence. The Agency has claimed it cannot document a
26 single example of therapeutic failure when an FDA-designated therapeutically equivalent product
27 was substituted for its reference (brand name innovator) product.^{1,6} Furthermore, the same
28 criteria for bioequivalence are applied to brand name products when they undergo formulation
29 changes. Like generic drugs, these reformulated brand name products are never tested in a
30 clinical population.

31
32 While concerns still persist among some physicians about the therapeutic equivalence of generic
33 NTI drugs to their brand name innovator products, scientific evidence to support these concerns
34 either does not exist or is extremely weak. In large part, studies reviewed and cited in this report
35 suggest “AB-rated” generic NTI drugs were bioequivalent to their brand name innovator products
36 in patients with diseases for which the drugs are indicated. Theoretical assumptions of the
37 possibility of inequivalence are not a sufficient basis for presuming its presence and acting on that
38 assumption. Anecdotal reports are similarly unhelpful, since one is often unable to distinguish
39 product failure from a natural change in disease process or patient response. Consistent with
40 current AMA Policy H-120.984, however, physicians should continue to report serious adverse
41 events that may be related to generic substitution to the FDA’s MedWatch program, and the FDA
42 should continue to pursue research to ensure the methodology to determine bioequivalence is
43 optimal.

44
45 Given the present evidence on the therapeutic equivalency of all FDA “A-rated” drugs, including
46 those with a narrow therapeutic range, the prescribing physician should be able to decide whether
47 a specific brand or generic drug product is most appropriate for the individual patient. Consistent
48 with state laws, third-party payers should not substitute a generic for brand name drug unless it
49 has been authorized by the prescribing physician. As stated in current AMA Policy H-115.994,
50 when a prescription for a generic drug product is refilled (e.g., for a patient with a chronic

1 disease), changing the manufacturer should be discouraged, whenever possible, to avoid
2 confusion for the patient.

3
4 For many drugs, especially those with a narrow therapeutic range, therapeutic drug concentration
5 or pharmacodynamic monitoring is necessary to assure the desired clinical response. Such
6 monitoring is necessary irrespective of whether the drug is a brand name or generic product.
7 In addition, patients must receive adequate education to be able to fully understand the nature and
8 proper use of their medications. As described in current AMA Policy H-115.974, this should
9 include appropriate education from the pharmacist if the generic drug manufacturer is changed
10 when the prescription is refilled.

11
12 RECOMMENDATIONS

13
14 The Council on Science and Public Health recommends that the following recommendations be
15 adopted in lieu of Resolution 527 (A-06) and that the remainder of this report be filed:

- 16
17 1. That American Medical Association (AMA) Policies H-125.984 and H-115.974 be
18 reaffirmed. (Reaffirm HOD Policy)
19
20 2. That our AMA inform the Centers for Medicare and Medicaid Services, America's Health
21 Insurance Plans, the Pharmaceutical Care Management Association, the National Association
22 of Boards of Pharmacy, the National Association of Chain Drug Stores, the National
23 Community Pharmacists Association, and the American Pharmacists Association about AMA
24 Policies H-125.984 and H-115.974, and that our AMA urge these payer and pharmacy
25 organizations to support these AMA policies. (Directive to Take Action)

Fiscal Note: \$500

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