

This is Section 2 of the fourth in a series of featured controversial articles, on medical, psychological, or related issues. I hope to stimulate discussion, letters, and interaction in Telicom and also possibly on outside forums, such as ISPE-net. I focus on the areas where the mythology may need to be broken and where limitations may not necessarily be recognized. This is the continuation of the first four parts of this article (Section 1). Both sections are written in a dialogic style. As with all publications, information such as this must be considered only after consultation with physicians and any medical information recorded here should not substitute for such consultations.

From Generic Substitution to Nutraceuticals: Control, Care, Countries and Choices (Section 2) **Vernon M Neppe MD, PhD, FRSSAf, DFAPA, BN&NP, MMed.**¹²

Abstract

*Generic substitution rules in the USA are carefully fashioned and stringent. The specific principles of bioequivalence of the generic compared with the original brand name drug is closely linked with therapeutic index. This ongoing project of maintaining generic efficacy without more toxicity than the brand name drug has allowed data evaluations, accumulating experience, and worldwide application of related principles. However, the balance of pharmaceutical industry drugs and their major role in the progress of medicine have created specific dilemmas for physicians and pharmacists. Diagnosis and the individual's sensitivity need be considered particularly with so-called "narrow therapeutic index" agents. The position is even more complex with so-called nutritional supplements where the extent of regulation is very variable and far less controlled than the generic.*¹

Keywords

80-125 rule, A products, Abbreviated New Drug Application (ANDA), absorption, allergy, Alternative Medications, area under the curve (AUC), arrhythmias, Australia, B products, bioequivalence, blood, branded generics, brand-name, Britain, Canada, carbamazepine, cautions, clinician, confidence interval, costs, critical dose drugs, crossover studies, dialogic style, different preparations, dosage, drug clearance, economics, efficacy, excipients, exclusivity rights, expiration, extended release, FDA, generic, Generic Initiative for Value and Efficiency (GIVE), Germany, good manufacturing practice (GMP) guidelines, Hatch-Waxman Act of 1984, herbal remedies, history, inter-individual variability, in-vitro, in-vivo, Israel, lamotrigine, layperson, maximum concentration (Cmax), medical education, mythical interview, narrow therapeutic index (NTI), Nutraceuticals, patent, patient, peak plasma concentrations, pharmaceutical alternative, pharmacist, pharmacodynamic, pharmacokinetic, phenytoin, physician, preparation, production, purity, quality control, responsibilities, scandal, sciction, seizures, side-effects, South Africa, studies, substitutions, therapeutic equivalence, toxicity, USA, vehicle, vitamins, warfarin, wrapper.

Generics: Review of Section 1 **Vernon M. Neppe**

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Introduction

Generic drugs, or *generics*, are approved as equivalent in active ingredients to the *original brand name drug*. The approval agency of the country such as the FDA³ in the USA, regards both generic and brand products as having ostensibly equal biochemical composition.⁴⁵ Generics are therefore considered equivalent substitutable products to the brand drugs; unlike most brand name drugs which average an exclusive patent for about a decade, generics are not usually patent protected.¹

Generic substitution has become the routine method of prescribing non-patented drugs world-wide because of the ostensible cost savings. The solution is not simple, however: Small variations in bioequivalence of the generic compared with the original brand name drug may produce significant clinical differences in efficacy and toxicity, compromising both the patient and the costs in the system. The pharmaceutical industry still play a major role in the progress of medicine. In Section 1¹, I examined the basics, the financial implications and some knotty problems (Parts 1 through 4). I continue here to use the dialogic style based on the genre of sciction² with different dyads in each part, more appropriately targeting different levels of readership providing a graded education on generics.

This paper adds detail and complexity and deals with the following issues:

- In Part 5, on Quality Controls, it's the Pharmacologist interchanging with the *Physician*.
- in Part 6, on Narrow Therapeutic Index, the Mythical Interview involves the *Critical Care Physician. interfacing with the Clinical Pharmacologist*.
- In Part 7, the USA and Beyond, the *Student* interfaces with *the Medical Historian Politician*.
- In Part 8, the interview involves *Intelligent Layperson Patient*, interfacing with the Physician who is additionally trained in nutritional supplements.
- And finally, in Part 9, the Mythical Interview involves the *Intelligent Layperson cum Patient interfacing with the Doctor* (speech in plain text).

Generic Quality Control (Part 5)

Vernon M. Neppe

Mythical Interview: Physician. Interfacing with the Pharmacologist.

What is the specific FDA rule for generic substitution?

In the United States, a generic can be substituted for a brand-name product based upon data that have demonstrated pharmaceutical equivalence and bioequivalence. The generic company does not need to prove that their compound is effective and safe (clinically equivalent) because that has already been done with the brand-name drug, only that they are biochemically equivalent with the brand product.

³ FDA is an abbreviation for the US regulatory medication body called the Food and Drug Administration.

⁴ http://en.wikipedia.org/wiki/Generic_drug

⁵ Rarely, the actual formulation is patented.

What is the process?

The generic company files an *Abbreviated New Drug Application (ANDA)*.⁶ This process does not require manufacturers to include preclinical and clinical data because this was already done during brand-name trials. The bioequivalence data are the critical information required for an ANDA review of oral or solid generic drug product dose forms. Manufacturers are required to be in compliance with current good manufacturing practice (GMP) guidelines.

Bioequivalence and therapeutic equivalence

What technically is bioequivalence?

Bioequivalence, or bioequivalent, is defined as the absence of significant differences in the rate and extent of absorption into the body of the active ingredient of the generic drug compared with the brand-name product under similar experimental conditions in an appropriately designed study.³

What kind of studies are done usually?

Most bioequivalence trials use a *crossover design* because there is a large variability in drug clearance *between subjects*, and the within-subject variation is usually small compared with between-subject variation. Non-crossover studies may be necessary if the drug or its metabolite has a very long half-life, repeated pharmacokinetic profiles are hard to achieve, or residual pharmacodynamic effects are relevant. Though it has been highly debated, it is generally accepted that single-dose, two-way crossover trials under fasting conditions are usually adequate for determining bioequivalence.⁴

I know that generics have the same bioequivalence as the brand. What does that mean?

This means they must be regarded as equally bioavailable—the rate and extent to which the active ingredient is absorbed from a drug product is the same *and* becomes available at the site of drug action. For oral preparations, this means mainly absorption from the stomach and duodenum, although technically if a drug is acting at the brain level, we are assuming the same amount of generic drug gets there as the brand, which may not always be true.⁵

Just one lot? Isn't that risky?

It would be risky. You want consistency between lots. So it's usually helpful testing at least 2 lots of the applied for generic to see they're consistent in their manufacture.

So this means they are bioequivalent?

Yes. They are pharmaceutically equivalent when studied under similar experimental conditions in either a single dose or in multiple doses because absorption of the drug is the same.⁷ Bioequivalence may sometimes be demonstrated using a lab standard, and other times through comparative clinical trials or pharmacodynamic studies. Also the half-life (how long it takes for 50% to be metabolized and/or excreted) of the drug can be so calculated.

How can you prove it?

The choice of how to study the drug to prove its bioequivalence is based on where it

⁶ Section 505 of the act.

⁷ based on the best judgment of the Division of Bioequivalence of the FDA.

acts in the body and the ability of the study design to compare the drug delivered to that site. One or more of four methods are used:

(1) pharmacokinetic (PK) studies using, e.g., blood concentrations with areas of the drug under the curve at various times and peak concentrations.

(2) pharmacodynamic (PD) studies, where one can measure endpoints of what the drug does (e.g. possibly blood pressure measures in an antihypertensive agent)

(3) comparative clinical trials in limited volunteers (e.g., ideally 24-36 adults with a mandated minimum of 12, both sexes, several ethnic groups, varying age [≥ 18]), and (4) in-vitro studies.

Is therapeutic equivalence of a drug the same as allowing generic substitution?

Different sides of the same coin, maybe? The FDA stresses therapeutic equivalence evaluations involve evidence-based scientific judgment. Generic substitution may involve social and economic policy administered by the states and is intended to reduce the cost of drugs to consumers.

What is this AUC aspect?

This is complex theoretical support of bioequivalency testing. It uses compartment analysis: The body is a group of compartments based on absorption, distribution, metabolism, and excretion of the drug. A plot of plasma concentrations of the level over time produces a polyexponential equation with the area under the curve (AUC) and the times to reach peak (T max) and its concentration then (Cmax). These factors are mainly dose and absorption dependent.

What about just using urine instead of blood?

Urine measures are sometimes possible, but not usually reliable, so they're not used.

But what about products used on the skin or by injection?

Same rule applied differently. The measurements reflect how quickly and how much is available at the site of action.

The 80-125 rule

Why the choice of the 20% less rule?

This is based on the opinions of FDA medical experts. This $> 20\%$ difference for each of the above tests was regarded as undesirable for all drug products.

But why 80% low and the 125% high? Why the difference?

Numerically, this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

Why only 90% of all drugs in a batch?

Statistically, a 90% confidence interval occurs for each pharmacokinetic parameter using ANOVA statistics. (The so-called Cmax and AUC). The confidence interval must lie entirely within the 80% to 125% boundaries. However, the mean of the study data almost always lies in the center of the 90% confidence interval, and usually close to 100% (a test/reference ratio of 1).⁸⁴ This data is log transformed, and effectively, the variation is less than 10% with that 90% confidence interval.

Can some new generic products that should pass fail these tests?

Yes. Bizarrely, it could fail to pass the bioequivalence criteria if the variability of the original comparison product is high or the bioequivalence study has insufficient statistical power because of an insufficient number of subjects. Paradoxically, a test product with low variability may pass the bioequivalence criteria even when there are somewhat larger differences in the average response. But overall, this system assures that these generics do not deviate substantially in performance from the reference product.

How do we know that?

It is likely so because the Office of Generic Drugs conducted two surveys to quantify the differences between generic and brand name drugs. In the first survey,⁹ the observed average differences between reference and generic products for AUC was 3.5%,¹⁰ and the results were almost identical in the second survey,¹¹ with Cmax being 4.3%. The current practice is to perform two one-sided statistical tests (0.05 significance level) to ensure there is no more than a 5% chance that a generic product not truly equivalent to the reference will be approved.⁴

Is everyone satisfied with the current generic substitution criteria?

No. This has been a source of concern. For example, Levy believes that both the trade and generic companies should be required to confirm continued bioequivalence of their products with periodic testing. Levy recommends changing the current 90% CI of 80% to 125% to a tighter range of 90% to 112% for drugs that are not subject to variable first-pass effects. He also recommends the introduction of meaningful product sampling methods, required reporting of failed bioequivalence tests, periodic bioequivalence retesting of currently available products, and proper validation of the upper and lower limits of in vitro dissolution standards.⁶

Exceptions

But are all generics the same?

No! And this is a big concern. There are multisource and single-source drug products. The FDA has evaluated for therapeutic equivalence only multisource prescription drug products¹², which usually implies generics available from more than one manufacturer. Sometimes this means a drug repackaged and/or distributed by another generic manufacturer. So we may see the same generic or different generics. There is a specially mandated therapeutic equivalence evaluations coding

⁸ Different criteria are sometimes used when demonstrating bioequivalence through comparative clinical trials pharmacodynamic studies, or comparative in-vitro methodology.

⁹ 224 bioequivalence studies submitted in approved applications during 1985 and 1986.

¹⁰ JAMA, Sept. 4, 1987, Vol. 258, No. 9

¹¹ 127 bioequivalence studies submitted to the FDA in 273 ANDAs approved in 1997, the three measures reviewed include AUC(0-t), AUC(0-inf), and Cmax. The average differences were + 3.47% (SD 2.84) for AUC(0-t), + 3.25% (SD 2.97) for AUC(0-inf), and + 4.29% (SD 3.72) for Cmax (JAMA, Dec. 1, 1999, Vol. 282, No. 21).

¹² approved under Section 505 of the Act

system to provide additional information on the basis of FDA's evaluations. *A products* have been demonstrated, whereas *B products* have not been adequately resolved. The system is complex, involving subclassifications, such as topical preparations, aerosols, suppositories, intramuscular medications, or a kind of dosage form like extended release capsules.

Are extended release generics easy to classify?

Not really. Even with the bioavailability studies, there may still be differences, primarily because extended-release products for the same active ingredient rarely have the same formulation. The FDA does not consider these different extended-release dosage forms even with the same active ingredient in equal strength as therapeutically equivalent unless equivalence has been specifically shown.

(Table A)

Table A: Criteria for Therapeutically Equivalent Drugs:	
(1) approved as safe and effective; (2) pharmaceutical equivalents as they	<ul style="list-style-type: none"> • contain identical amounts of the same active drug ingredient • in the same dosage form and route of administration, • meet standards of strength, quality, purity, and identity
(3) bioequivalent as they	<ul style="list-style-type: none"> • do not present a known or potential problem and meet an acceptable in vitro standard (in a lab), or • if they have a potential problem, they meet an appropriate standard
(4) adequately labeled; (5) manufactured in compliance with Current Good Manufacturing Practice regulations.	

As an aside, are these stringencies ever waived?

Rarely but possibly. The first situation occurs when the in vivo (live patient) determination of bioequivalence is self-evident allowing a waiver of the in vitro (in the lab) methodology based on the best judgment of the Division of Bioequivalence of the FDA. In vitro determinations alone are insufficient for an approved ANDA.

Pharmaceutical Alternatives

I have heard the term "Pharmaceutical Alternative". What does that mean?

These drugs contain the same therapeutic moiety—the same important active chemical—but they are different salts, esters, or complexes or come in different dosage forms or strengths.

For example?

The antibiotic tetracycline hydrochloride 250mg capsules compared with a very similar variation with a different salt, namely tetracycline phosphate complex 250mg capsules.

What is the core of such a "Pharmaceutical Alternative"?

Here the FDA cannot prove the capsule is bioequivalent, and even different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.⁴

Now when are they "Therapeutic Equivalents"?

Only if they are both pharmaceutical equivalents with the same active ingredient as the brand-name drug and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling—they are bioequivalent, properly labeled, and appropriately manufactured as well as being safe and effective. The FDA believes that these products can be substituted with the full expectation that they will produce the same clinical effect and safety profile as the prescribed product.⁴ Therapeutic equivalence determinations are not made for unapproved, off-label indications.

Do physicians know about all of this?

Apparently, not well. A USA physician survey showed only one sixth of prescribing physicians correctly identified the FDA's standards for bioequivalency of generic drugs.⁷ A recent development to address the issue enables interested doctors and consumers to check generic drug interactions and provide outcomes to the specific drug and drug company.¹³

What are the responsibilities of the physician and pharmacist?

Professional care and judgment requires awareness that products differ in other characteristics besides therapeutic equivalence. There is a potential for patient confusion due to differences in color or shape of tablets and inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. One product may be more stable over another under adverse storage conditions, and a potentially important difference is allergic reactions may in rare cases occur due to the vehicle the drug is in or its coloring or preservative ingredient.

Anything else?

Yes. The practitioner should be aware of the differences in cost to the patient. The doctor and pharmacist still must prescribe and dispense products with due care, with appropriate information to individual patients, and with awareness of the characteristics of the vehicles being important in the therapy of a particular patient. Pharmacists should, of course, be familiar with the expiration dates and labeling directions for storage of the different drugs, particularly reconstituted products, to assure that patients are properly advised when one product is substituted for another.

Narrow Therapeutic Index Drug Generic Substitution (Part 6)

Vernon M. Neppe

Mythical Interview: Critical Care Physician interfacing with the Clinical Pharmacologist.

What are narrow therapeutic index (NTI) drugs?

¹³ Generic drug interaction checker and monitor

NTI drugs are defined as those drugs for which a 20% or smaller change in dose, with bioavailability remaining constant, can cause increased adverse effects, decreased therapeutic effects, or excessive therapeutic effects. The 20% figure is based upon the current bioequivalence standards of a 90% CI of the extent of absorption, as reflected by the AUC within 80% to 125% of the brand-name product.⁸

Does the FDA use the term?

Strangely, not. *NTI* is not a formal designation of the FDA. The FDA uses the designation of narrow therapeutic ratio. Essentially, the drug formulation is used to treat a critical acute or chronic condition; that the drug formulation is associated with a risk of toxic reactions, complex drug-drug interactions, or steep dose response curves; that the drug formulation has highly individualized dosing requiring continuing dose supervision by the prescriber to ensure its safe use; or that there is a competent medical determination that a lack of bioequivalency could have a serious adverse effect in the treatment or prevention of a serious disease or medical condition.

Which drugs are regarded as NTI ones?

Expert drug-specific interpretations establish the magnitude and types of increased adverse effects and altered therapeutic intensity warranting the *NTI* designation.

Who supports the NTI classification?

The pharmaceutical companies with brand-name products facing generic substitution. Potentially serious problems can also arise from pronounced variations between individuals in the pharmacokinetics and pharmacodynamics of many drugs.

Is this definition accepted?

No. Many pharmacists cannot agree on a common definition. They range from "drugs for which relatively small changes in systemic concentrations lead to marked changes in pharmacodynamic response"¹⁴ to drugs with a narrow therapeutic window between the minimum effective exposure and the maximum tolerable exposure to a drug.¹⁵ Essentially, relatively small change in systemic concentration can lead to marked changes in pharmacodynamic response.⁸

Surely generic substitution of narrow therapeutic index (NTI) drugs is problematic?

This is a complex issue that has changed over time. But the FDA does not recommend additional testing when a patient is switched from a brand-name to a generic product

There is a special kind of NTI drug, is there not?

Yes. One subgroup is called *critical dose drugs*. They require careful blood level or other monitoring, have serious clinical consequences in the event of overdose, and manifest a steep dose-response relationship. Examples of critical dose drugs include the anticoagulant warfarin, the heart rhythm drug digoxin, the anticonvulsant phenytoin, and the immunosuppressants cyclosporine and tacrolimus.

But are the decisions logical?

¹⁴ Benet and Goyan in Haveles, 2002

¹⁵ Patnaik et al. n Haveles, 2002

They are certainly ingrained. Clinicians and pharmacists have often made the decision about generic NTI drugs based upon information that is 20 years old. Many of the products have been historically viewed as “classic” medications, which were rarely substituted with the generic version.⁸

What about the guidelines? Should they be revised?

Some clinicians feel that there should be more rigid bioequivalence guidelines for NTI drugs. Others feel the bioequivalence requirements for NTI drugs should be based on intrasubject variability as well as pharmacokinetic-pharmacodynamic relationships.

And what is the prevailing opinion?

The FDA believes that based upon current prescribing standards, the requirements for NTI drugs may be adequate.

What criteria would reflect an NTI drug?

Williams⁹ delineated that either they have only twice the difference between effective and lethal median dose or only twice the difference between minimum effective and toxic blood concentrations. Both would require careful titration and monitoring for safety and effectiveness.

Have any NTI drug generics failed representing a public health hazard?

Not according to the FDA research.¹⁶ However, there is major controversy in the various states and there are frequently mechanisms in place to prevent such substitutions.^{10, 11}

So what are any differences attributed to?

Any increase or decrease in symptoms or an increase in toxicity may be a result of the patient paying closer attention because of the switch to the generic product.

So what would be sensible here?

Possibly that NTI drugs require frequent adjustments in dose and careful patient monitoring irrespective of the generic or brand-name product. The FDA may also recommend additional tests or approval of brand-name and generic products depending on the complexity of the drug product and whether or not small changes in dose or blood concentrations could result in changes in safety and efficacy.

The classic drug mentioned is always Dilantin (phenytoin)?

Yes, this is so, as it has a particularly small range between therapeutic and toxic levels. Yet, about five million prescriptions of generic extended-release phenytoin sodium (Mylan) have been dispensed since May 2001, with only 63 lack-of-effect cases reported to the FDA, and 23 were thought to be caused by other factors.⁸

So where are we now?

The FDA supports the substitution of generic drugs with “A” ratings for the corresponding brand-name products. Recent pharmacokinetic trials of several NTI drugs have demonstrated bioequivalence and therapeutic equivalence with the brand-name product and like all other approved generics have achieved an FDA rating of “A,” meaning they’re acceptable.

Generic Substitution—the USA and Beyond (Part 7)

¹⁶ The FDA performed postmarketing testing: More than 400 samples of 24 brand-name and generic products were tested and found to meet established standards of purity and quality. Further investigation by the FDA has found no problems attributed to generic substitution.

Vernon M. Neppe

Mythical Interview: Student. Interfacing with the Medical Historian Politician.

History

I always find a historical perspective helpful as to why the regulations exist. What happened at the turn of the 20th century?

Nothing. The modern era of drug control happened in 1938.

So what has happened to these drugs before 1938?

These drugs are still around. They're marketed, but approved only on the basis of safety as covered by the ongoing review.^{17 4}

What changed after 1938 in the USA?

The drug required a special FDA application with an effective approval that was not later withdrawn for safety or efficacy reasons. (This is independent of any current regulatory action through administrative or judicial means against the drug.)⁴

When did the FDA begin generic marketing?

FDA was given statutory authority to allow the marketing of generic versions of those brand-name products approved after 1962 as safe and effective.

When did bioequivalence data accumulation really begin?

There was insufficient bioequivalence data which changed in the late 1960s. Before that, drugs prescribed were automatically given as brand-names.

When did the states begin to adopt the same in attitude towards generics as the FDA?

In 1979, the FDA provided a single list based on common criteria, instead of using state laws that differed in definitions and criteria.¹⁸ This way, the FDA did not serve the needs of each state on an individual basis.

Are all states the same in attitude towards generics in the USA?

Yes. It seems that every state has now adopted laws and regulations encouraging generic substitution. However, they vary in detail. The laws, in general, require either the positive formulary approach—that substitution be limited to drugs on a specific list—or the negative formulary approach—generics are permitted for all drugs except those prohibited by a particular list.^{4 19}

What is the key USA act about generics?

¹⁷ Drug Efficacy Study Implementation [DESI]

¹⁸ See the Federal Register on January 12, 1979 (44 FR 2932) for the background and basis of FDA's therapeutic equivalence evaluation policy and the public comments on the proposal of the Federal Register on October 31, 1980 (45 FR 72582). In October 1980, the final version of the FDA Drug List incorporated appropriate corrections and additions. Each subsequent edition has included the new approvals and made appropriate changes in data.

¹⁹ The FDA included only currently marketed approved prescription drugs, either new drug applications (NDAs) or abbreviated new drug applications (ANDAs) under the provisions of Section 505 of the Act. (January 1979)

In the USA, the so-called Hatch-Waxman Act of September 1984²⁰ describes the procedure for an Abbreviated New Drug Application (or "ANDA") with the FDA demonstrating therapeutic equivalence to the specified, previously approved "reference listed drug." When the ANDA is approved, the FDA adds the drug to the "Orange Book" of Approved Drug Products subclassifying the drug's equivalence within specific therapeutic groups.²¹

If my memory serves me correctly, there was some kind of scandal?

You're right. There was the "generic drug scandal" of 1989 and 1990, when investigators revealed corruption within the generic drug industry. Companies representing 75% of the generic production industry pled guilty to filing false applications with the FDA and paying illegal gratuities or other related unfair competitive advantage crimes. This set back generic substitution profoundly.

What is the most recent advance in generics?

The Generic Initiative for Value and Efficiency (GIVE) initiative of 2007 uses existing resources to assist the FDA in modernizing and streamlining the generic drug approval process.²²

Why is all this done?

As the FDA says: for "public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs."⁴

Are the laws for physicians prescribing and pharmacists dispensing generics, the same in all of the USA?

No. The laws in each state of the USA are minimally different. So are the terminologies. This creates a situation where legal requirements for patient and physician responsibility differ slightly.¹² In some states, e.g., unless the prescription reads e.g., "*Do not substitute*" or "*Brand Name Only*", the pharmacist can substitute. In others, the physician may write "*Dispense as written*". Thus often the physician has to choose or mandate. But in some states, the patient can choose specifically the brand name even on a generic prescription.

Other countries

I understand that the generic regulations were led by these rules in the United States.

This is likely so because the costs of pharmaceuticals were so much higher in the USA then elsewhere.

So what has been happening elsewhere? I don't need dates just a perspective.

Yes I can give you a few flashes on this subject.

Does the term generic mean the same?

²⁰ September 24, 1984: the Drug Price Competition and Patent Term Restoration Act (1984 Amendments) with regular amendments occurring thereafter to ensure currency.

²¹ The Orange book refers to the publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* produced by Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act. The Preface contains an explanation of FDA terms and procedures

²² October 4, 2007

Not completely. The term *generic drug product* has different meanings in different countries. Marzo and Balant suggest that the phrase "interchangeable multisource pharmaceutical product" may actually be a more appropriate term⁸, though it is cumbersome to say.

What about experience with generics in other countries?

Policies implemented in the countries with a high rate of generic drug use, such as Canada, Denmark, Germany, the Netherlands, the United Kingdom, and the United States, reflect savings through increases in the volume of generic drugs used and the frequently significant differences in the price between generic medicines and branded originator medicines. In all countries, quality control of generic drugs is critical. Policy tools include both accounting for supply-side and demand-side measures. On the supply-side, key measures are generic drug marketing regulation that facilitates market entry soon after patent expiration, reference pricing, the pricing of branded originator products, and the degree of price competition in pharmaceutical markets. On the demand-side, prescribing and dispensing patterns and differential co-payment structure for consumers and patients is a pre-condition for all other measures discussed to take effect.¹³

What about patient attitudes?

Germany: Nearly two thirds of patients in a German study stated that they knew of the difference between brand-name drugs and generics; of these, one third were not satisfied with the information given by their GPs, and 37% of patients expressed general skepticism towards generic drugs because of their lower price. This attitude was more frequent among those who felt that generic prescribing was "invented" to solve the financial crisis in the German health insurance system at their expense. Patients who had been skeptical when first confronted with a generic substitution were more frequently among those who considered inexpensive drugs to be inferior. The patient view that inexpensive drugs must be inferior may be difficult to rectify in the short term.¹⁴

How does the law differ elsewhere?

Canada: In May 2004, Canada's Parliament amended the Patent Act to provide for the compulsory licensing of patented pharmaceutical products, which allows generic manufacturers to make cheaper, generic versions of patented products and export them to countries that do not have sufficient capacity to produce their own.¹⁵

South Africa: Generic products sometimes try to enter the market prior to patent expiration by incorporating different salts of an approved active pharmaceutical ingredient (API) in a brand company's marketed dosage form and subjecting these new drugs to bioequivalence assessment. These challenge current regulatory authorities to approve as bioequivalent products containing these *pharmaceutical alternatives*, as there may be modifications of safety and efficacy and a question of their generic substitutability.¹⁶

What about stockpiling?

Australia: In view of the possibility of a human pandemic of avian influenza, a first-line strategy for many countries is stockpiling of antiviral neuraminidase inhibitors (oseltamivir [Tamiflu] and zanamivir [Relenza]), which can reduce mortality, morbidity, and influenza transmission. However, global supply of the antivirals is controlled by the European-based patent owners Roche and Glaxo Smith Kline. This prevents competition in the manufacturing and distribution of antivirals and has reduced global supply capacity and affordability. The Australian Government has acknowledged that, in the event of a pandemic, its own stockpile of antivirals will be limited and reserved for those on a confidential rationing list. Pharmacies are running out of stocks, limiting opportunities for individuals to secure supplies privately.¹⁷

What about symptoms from generics?

Canada: There are potential risks posed by a switch, e.g., Celexa to generic citalopram. In an Anxiety Disorders Clinic, patients who were unknowingly switched to generic citalopram from Celexa in Quebec, Canada and experienced a re-emergence of their anxiety symptoms or development of new adverse events are described in this case series report. All patients reestablished previous treatment response with a change back to Celexa.¹⁸ Whereas this is not common, it is important for clinicians to be aware of the potential for loss of treatment effect or symptom re-emergence posed by a switch to a generic agent. Randomized, double blind, controlled investigations would likely provide useful information, as current bioequivalence and pharmacological equivalence do not necessarily translate into clinical equivalence.

But is this an isolated instance?

Not really. Similar findings have occurred in antiseizure medication in Quebec, where compulsory generic substitution of antiepileptic drugs (AEDs) in Canada may lead to adverse effects in epilepsy patients because of seizure recurrence or increased toxicity. The switchback rates from generic to brand-name anticonvulsants are high: About one eighth of patients switched back to Lamictal (11.7% monotherapy, 13.4% polytherapy), and with Depakene (valproic acid), one fifth. These results reflect poor acceptance of switching AEDs to generic compounds. They may also indicate increased toxicity and/or loss of seizure control associated with generic AED use.¹⁹

Israel: A similar view is expressed: In general, cost-effective seizure control should not be sacrificed on the basis of cost alone, as the major end point in treating epilepsy with AEDs is seizure control without side effects. Until we have individual (within patient) bioequivalence data on generic AEDs and/or the tools to a priori identify the subset of patients susceptible to the generic switch, a switch of AED products in seizure-free patients is not recommended.²⁰

What about shelf life?

Poorer countries: Then there are the problems of the shelf life of drugs. That shelf life again varies depending on the particular medication, the kind of formulation—you would imagine that liquids are far more difficult than solids to maintain in a proper format—and it may vary by country. But because the vehicles are not the same generic drugs may also not have the same shelf life. At times, one finds the practice of donating medications to poorer countries, and very often these are expired samples. This is a rather paradoxical situation because they may not be good enough for those, e.g., in the United States, but may be good enough for those in Africa. The

reality is very often one can examine these expired medications and notice there is no change in terms of color and the drugs are not crumbling and the drugs look good. They may well be good, it's just certain limits have to be set in terms of whether or not that is appropriate, so it cannot be recommended that one has the drug beyond time of expiration. Although this in our experience had been common practice for patients to do, but if those drugs go off, one sees loss of efficacy.

Are nutritional substances riskier than generic substitution? (Part 8)

Vernon M Neppe.

***Mythical Interview: Intelligent Layperson Patient* interfacing with the Physician who is additionally trained in nutritional supplements.**

A major consideration of consulting your physician is to optimize the assessment of your difficulties and manage your condition appropriately.²³ A high proportion of patients ostensibly take nutritional substances in addition to their medication.²⁴

I take vitamins and all sorts of compounds for health as opposed to disease. What is the technical name for them?

Today, it is common for patients to be taking "Alternative Medications" or "Nutraceuticals," such as herbs, minerals, vitamins, diet pills, and synthetic chemical supplements with prescribed medications. We recognize that these Nutraceuticals may be valuable drugs, but they also have their dangers, including when they are taken with prescription medications. These are outlined below, as the choice of whether to take these Nutraceuticals rests ultimately with the patient, not the physician. Physicians are not specialists in Nutraceuticals.

Consequently, this section clarifies briefly, and incompletely, the difficulties of taking such "Nutraceuticals". The term "Nutraceutical" is used synonymously here with "Nutritional supplement," and this includes also "Diet supplement" which is, therefore, a group of "Alternative Medications".

So herbs and special natural chemicals are also classified as Nutraceuticals?

Indeed. Using herbs like St. John's wort, Echinaceae, Grape-seed extract, Melatonin, and Ginkgo biloba, as well as chemicals such as SAMe and glucosamine have become a significant practical option amongst patients. The growing use of special "diet" drugs with numerous different compositions complicates such aspects further. Similarly, weight loss has become extremely important amongst many who are overweight. Many different herbal and over the counter formulas and nutritional solutions are suggested. The lay public is bombarded with "information" which may be disinformation.

²³ This document was developed in consultation with a special committee of the American Society for Clinical Psychopharmacology (ASCP) during 2000. A major source for information for this document is the book, *Cry the Beloved Mind: A Voyage of Hope*, and more specifically Chapters 7 and 8, by Dr Vernon M Neppe (see <http://www.brainvoyage.com> for more details). This discussion is not intended as, nor must substitute for the professional judgment of a physician or other health care provider. No responsibility, by omission or commission, can be taken for decisions to take or not take any Alternative or other medications.

²⁴ This article section is based on Pacific Neuropsychiatric Institute (PNI) Pacific Neuropsychiatric Institute and Vernon M Neppe MD, PhD, Seattle, WA. 2003. <http://www.brainvoyage.com/supplements/cautions/> ©

Where does this fit into generics?

These Nutraceuticals are invariably not patented and most do not have detailed controlled, double-blind studies analyzing efficacy, risks, and side-effects. Often they are not regulated, and therefore, we cannot even talk about bioavailability.²¹ So if we have problems with generics, how much more so these Nutraceuticals?

And I suppose they can interact with prescribed medications?

Indeed. The problem is usually this involves prescription of medications in the correct dosage and combinations, and these are as much "medications" as the prescribed ones in that they interact.

What proportion of patients actually take these medications?

Figures are hard to get. This is so, as many patients do not like to talk about it because their physicians may be less than delighted, or they don't think it's worth reporting. So it is likely underestimated.²¹ We know that a significant proportion—probably a majority depending on the population analyzed—of patients consulting physicians may inquire about or take Alternative Medicines, either alone or in addition to their current medication.

So are they bad?

No. They may be great. But only sometimes when these have therapeutic value. At other times they don't have therapeutic effects, but this does not mean to say they will not work for other indications. The whole area needs scientific control and scrutiny as well as empathic understanding. Studies on herbal products are not done using the stringent criteria that regulatory bodies, such as the American Food and Drug Administration, require prescription drugs to go through, nor do they go through the same approval process. Many prescription medications derive originally from plants, though today synthetic preparations are easier and often better.

So supplements can be taken?

Fundamentally, I don't have problems with people taking herbal medications, provided they sensibly observe the changes that are happening to them and exhibit as much care and respect towards potential problems as they would while taking a prescription medication. Another provision exists: They must realize that the well-tried and trusted, researched prescription drugs may also have been herbs in their primitive days. But they now are refined, and their benefits have been shown to outweigh their risks. The herbs they're taking may ultimately be shown to be food or poison.⁵ They should also inform their pharmacist and physician of this so they can screen for any interactions.

This is why I thought I'd take supplements instead.

But they're medications as well, although they're not controlled medications. We don't know the right doses; we don't know their appropriate indications; and we don't know the purity of the preparation. They are still medications because they have potential pharmacological effects—they're just inadequately studied drugs. In fact, they may even be more dangerous than regular prescribed drugs because of the many unknowns, impurities, and variabilities in potentially toxic compounds.⁵

What are the problems then?

Because something is supposedly a "natural" substance, like a natural herb, doesn't mean to say that it's completely harmless. Snake venom is natural. Herbs have

pharmacological activity. Herbal treatments and other alternative medications such as synthetic chemicals may produce problems. This is not to say that there may not be a therapeutic value to any specific Alternative Medication. It is important always to weigh the risks with the benefits. The benefits may relate to the potential value of the compound for any individual. Such benefits may be based on research and clinical knowledge as well as the individual's specific experience with the compound. The risks may similarly be based on accumulated research, clinical and individual data, but can also be delineated below.

Why should we be cautious?

Below are several reasons recommending caution when using Nutraceuticals. There may be others, but these seem amongst the most cogent. There are many cautions which we are aware of for the use of regular prescribed medications, but these generally are listed in the package insert. There do not appear to be FDA approved, regulated package inserts (equivalent to prescribed drugs) available for Nutraceuticals. However, please bear in mind that even though these are general principles, this does not mean that any specific Alternative Medication is necessarily bad. The good may outweigh the bad.

How regulated are these Nutraceuticals?

Generally, they are not. First, herbs and other Nutraceuticals are not as well regulated as prescription medications. We often do not know about the purity of the preparation, the consistency of batches of the same preparation, the correct doses, or their appropriate indications. These drugs may have potential pharmacological effects, but are frequently inadequately studied. This may mean that they could even be riskier than regular prescribed drugs because of their many unknowns, impurities, degree of stability of batches, and other variabilities.

Are they pure?

Often not. For example, herbal remedies are often not single chemical preparations. There usually is an active chemical inside them, but we may not even know what it is. For example, there is still debate what the active ingredient of St. John's wort is. This creates a situation where different chemicals, some unnecessary, may interact with each other.

Are their effects proven?

Often not. With some of these Nutraceuticals, we're not even sure whether a placebo—a drug without therapeutic effect such as a sugar—won't not work as well. This is because they have often not appropriately been studied to demonstrate added therapeutic benefit over and above what placebo would show.

But there should be few side effects surely?

This is variable. They might have side effects due to the active chemical compounds. Common side effects may be irritation of the stomach, sleepiness, or anxiety. Not even vitamins are always safe. Some vitamins are toxic in too high a dosage, like the fat-soluble ones, vitamin A and vitamin E. The side effects may not be immediate or short-term: Instead, they may be noted only after many years.

Do Nutraceuticals have side-effects?

Yes, in part. In both, the side effects may not be due to the active chemical. It may be due to the vehicle—the wrapping around the drug—and not the herb or prescription medication or vitamin itself. For example, even the apparently innocuous

drug L-tryptophan (a component in foods such as milk) produced a potentially fatal reaction probably because the vehicle produced an allergic reaction. The vehicle can vary greatly from one preparation of the same medication to another and might increase or decrease drug absorption. If the compound absorbs too quickly, unpleasant side effects may occur because the blood level increases precipitously. But if it is absorbed too slowly, it could cause nausea or diarrhea, especially if the drug is not absorbed, and then the medication will not work as well. Different parts of the gastrointestinal tract may be involved; a capsule might be absorbed differently from a tablet; and a particular long-acting preparation will vary from the shorter-acting one. We see these problems with prescription medications (brand and generic) as well, but these approved preparations are generally better controlled.

So essentially Nutraceuticals don't even have the controls that generic drugs have? Indeed, not. They are far less regulated. So actually, patients must be more careful.

So presumably the active ingredients can also be problematic?

Yes. But not only because of variations in biochemical composition as with the generics versus brand-name drugs. Because the active ingredients of these herbal remedies are as yet inadequately studied chemicals, we do not know what interactions will occur with other medications. These could relate to absorption from the stomach or other parts of the gastro-intestinal tract, as well as metabolism in the liver, and sometimes even to binding of proteins. Moreover, foods may be involved: For example, St. John's wort may, theoretically, produce a dangerous food reaction called the "tyramine effect," or another compound, Gingko biloba, may, in practice, interact with anticoagulant medication like Coumadin.

And I'm assuming that this would happen, too, because of inconsistently taking such Nutraceuticals?

True. When taking Nutraceuticals like herbs, irregularly, not on a daily basis, at a different time from other medications, there may be reduced interactions in absorption at the stomach level, but there may still be some inconsistency with absorption of regular prescribed medications. When taking Nutraceuticals regularly, at a regular time and under consistent conditions, e.g., before meals, any absorption interactions may be more consistent. However, interactions at the liver level may occur in any event, and an increase or decrease or unchanged levels of prescribed medications may result. Conversely, the Nutraceuticals may be altered, or there may be changes in absorption or effects. We are unaware of how many vitamins, minerals, herbal products, and synthetic chemicals are going to interact with medications. Absorption and metabolism is also sometimes a problem with regular prescribed medications. We are gradually building up a body of knowledge, in this regard, but there are still numerous unknowns.

But then there seems to be another difference from generic where we know what dose to take ...

Yes, often dosage of these Nutraceuticals—non-prescription drugs—is questionable. E.g., melatonin was marketed for sleep at much too high a dosage 3 mg or 6 mg a day—when the physiologic dose may be half a mg a day. The problem, however, is different absorptions producing a question as to the correct individual dosage. Different preparations may vary enormously. Even more so, *labeling also varies*

enormously: Some Nutraceuticals list the number of milligrams of plant substance (root, leaf, or stem), while others list the number of milligrams of the active component of the plant. This could potentially produce patient, physician or pharmacist errors.

I'm assuming, in any event, that because these Nutraceuticals have chemical effects the interaction can be harmful?

True, it is possible that Nutraceuticals may in some way change the way some prescription drugs are working. They may amplify some effects; they may neutralize some effects; or they may modify them: This can have adverse consequences, so that specific prescription drugs may not work properly.

What about pregnancy? Surely they're safe there?

Not true. It is possible that these Nutraceuticals could cause problems in pregnancy or during breast-feeding. They have generally not been studied in that regard. Now this applies with generics too, but that's dependent on any difficulties demonstrated with brand-name drugs.

I would think herbal remedies would amplify these problems?

Possibly: Different tablets or capsules of the herbal remedy might have different levels of the relevant active chemicals. Even when those differences are subtle, that might make a big difference. This is because there are less stringent requirements than producing a prescription drug.

When medications be they generic or not, are given for years, we usually have data that they will continue to work. Does the same apply to Nutraceuticals ?

No, we don't know whether even Nutraceuticals like a herb that has been demonstrated to have a therapeutic effect will maintain that effect over time. We also do not know whether chemical changes in one's body or one's brain may not require habituation to the chemical even after it has lost its effect. When you take Nutraceuticals, you should carefully and sensibly observe the changes that are happening to you and exhibit as much care and respect towards potential problems as they would while taking a prescription medication. The herbs you taking may ultimately be shown to be food or poison.

So what guidelines should I use if I'm using regular generic or brand name medications and want to use these Nutraceuticals ?

1. A "safe" way to avoid interactions may be to avoid taking new Nutraceuticals with your prescription medications. However, this has the limitation of not receiving any therapeutic value these Nutraceuticals may have in your particular case.
2. On the other hand, just stopping the Alternative Medication you are taking may result in withdrawal effects or loss of the therapeutic effects of these drugs. If you choose to withdraw off these Nutraceuticals, it sometimes may be necessary to gradually taper over several weeks. However, every chemical is different and such a taper may also run the risk of side effects and drug interactions, and there are times when it may be preferable to go off the non-prescription drug immediately.
3. Your third choice may be to take the Nutraceuticals in conjunction with your current medical prescription drugs. In this instance, you do not lose the benefits that the non-prescription Nutraceutical provides for you. However, this involves risk,

including those listed above. You should regard such compounds understanding there may be benefits and risks.

Whose choice is it?

The choice as to whether to take Nutraceuticals is yours alone. We medical practitioners cannot take responsibility for your taking them. We cannot guarantee the safety of any of these alternative compounds, nor their potential drug interactions. Even when medical doctors assist you or guide you in making that choice, you must understand there is a great deal that is unknown or contradictory and uncertain in this area and that your physician who is not specifically trained in Nutraceuticals—may not necessarily know about the side effects and interactions and the specific preparations—even the well-documented ones—of the specific Nutraceuticals you are taking, considered taking, or may have taken. You should, nevertheless, endeavor to keep your physician current as to any medications and Nutraceuticals you are taking. You are free to disregard the advice above, but at least think about it.

Taking Nutraceuticals is taking them at your own risk. The choice is yours.²⁵

So are nutritional substances riskier than generic substitution?

Yes. You can see that there is an added component of the unknown: Interactions, quality control, side-effects, long-term effects, and possible negation of other drugs are all not explored. Still there is a place for these compounds but after appropriate consultation only.

Generic Substitution or Brand Drug: Perspective (Part 9)

Vernon M. Neppe

Mythical Interview: Patient (speech in italics) asking the Doctor (speech in plain text).

So what is the bottom line? Generic or brand drug?

Both have their own roles.

Branded drug...when?

When we want to be particularly careful because of the patient's potential life-threatening acute condition; or a tendency to allergy where the actual chemical is irreplaceable; or cross-allergy may cause problems; or the drug has a low range between therapeutic and toxic doses, we may tend towards brand name drug.

So it's the drug and the condition and the patient in combination?

Yes. We, therefore, are more careful with narrow therapeutic range drugs and need to monitor the patients more carefully. It is controversial whether the rules should be any more special for these drugs.

But generics save the economy?

Indeed. When we realize the enormous care taken in making generics as equivalent as possible, and when we perceive the potential costs saved to patients, to the insurance, and to the economy, generic drugs are logical.

²⁵ This document is meant as a guide only to information and accuracy cannot be guaranteed. The document is not intended to provide medical consultation regarding the diagnosis, management or treatment of any patient.

I know there are many different types of drugs?

True. I list this in Table B below. And Nutraceuticals too which also can interact and cause problems or help. Only "approved prescription drugs with therapeutic equivalence" are "prescription generics" of branded compounds. But it doesn't mean that over the counter drugs (OTCs) do not also cause problems, and these may be generic substitutes of previously prescribed branded drugs.

Table B: The 4 subclassifications of drugs^{4*}

- (1) approved prescription drugs with therapeutic equivalence
- (2) approved over-the-counter (OTC) drugs for those drugs not covered under existing OTC monographs;
- (3) approved drugs administered by the Center for Biologics Evaluation and Research
- (4) approved products that have any of:

- a. never been marketed
- b. for export
- c. for military use
- d. have been discontinued from marketing,
- e. have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing.

* Not specifically in the FDA classification above are so-called nutritional substances (Nutraceuticals) although they could fit the OTC group.

And any different generic drugs dispensed to the same patient can cause problems?
Indeed! Sometimes problems are not due to a specific generic but because the generic was switched and a patient who was taking 100mg daily for years suddenly is receiving a preparation making his dosing 85mg daily.

So how do we know which generic batch we've received?

A good pharmacy will mark the exact generic version name and / or the national drug code (NDC) number on the bottle. In the USA, we can go to a site like <http://www.fda.gov/cder/ndc/>. This way we can trace the exact label and product codes and where the medication comes from.

And does this happen outside the USA?

It does but variably. Many countries have a National Formulary and have ways to trace medication batches. This is very important as some medications may need emergency calls.

Therefore generics impact markedly on the world economy?

Yes, it seems where-ever we now go in the civilized world, we encounter the use of generics. They literally allow mankind to afford drugs.

But homage is in order?

Certainly. Remember that without the parent brand drugs in the first place, none of this would be possible. Instead, we would still be hovering in the middle-ages because our economies, in general, would not be supporting the enormous costs of marketing drugs.

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