

This is 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 This article has several parts, written in a dialogic style, and because of its length is divided into Sections, appearing in consecutive issues of Telicom. 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.

A Voyage into Generic Substitution (Section 1)

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Abstract

Generic substitution has become the routine method of prescribing non-patented drugs world-wide because of the ostensible cost savings. Despite stringent, but at times controversially liberal, FDA rules, the balance at times is somewhat precarious: 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 original brand-name pharmaceutical industry drugs still play a major role in the progress of medicine.

Keywords

80-125 rule, absorption, allergy, arrhythmias, bioequivalence, branded generics, brand-name, Canada, carbamazepine, cautions, clinician, conversagraph, costs, dialogic style, different preparations, dosage, drug, economics, efficacy, excipients, exclusivity rights, expiration, extended release, FDA, generic, lamotrigine, layperson, medical education, mythical interview, patent, patient, pharmacist, phenytoin, physician, preparation, production, purity, responsibilities, sciction , seizures, side-effects, studies, substitutions, therapeutic equivalence, toxicity, USA, vehicle, wrapper.

Generics: Introductory Perspective (Part 1)

Vernon M. Neppe

Introduction

An extremely important area of medical practice has been the substitution of brand name drugs with generics. Brand name drugs are generally the medications that have been researched in detail and are patented. These drugs are approved by the Food and Drug Administration (FDA) and have become the life-blood of extended medication treatment, as well as initial management. These branded patented drugs frequently reflect advances in treatment: They are generally exclusively available for a decade, or perhaps a little longer. This is despite an extended period of time associated with research and development, which may take a decade-and-a-half.

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^b © VMNeppe 2008.

Exact duration of time of the patent is variable depending on the country and the exact legislation. Hundreds of millions of dollars are often poured into such drugs, and this is small change when one considers that possibly tens of drugs may be developed for each single drug that makes it to the market. This paper deals with key questions such as: Is it appropriate to use generic drugs all the time? Should I just be using brand name drugs if I can afford it? When would there be exceptions to these rules? Are generics really entirely equivalent?

The controversy:

The whole area of generic substitution is so complex that to simplify it I've chosen below to use a composite dialogic sciction style, whereby the expert physician and pharmacologist answers the questions of an intelligent layperson.

The style:

I've written this article in several parts. Each part contains a dialogic style which is based on the genre of sciction¹ that I first developed in *Cry the Beloved Mind: A Voyage of Hope*.^c In fact, some of the dialog is modified from that book. However, this dialog is implemented purely as an easier means for education, the questions are obviously based on composite realities, but the characters are not developed. It's like a television interviewer discussing different levels with the interviewer in italics and the interviewee in regular case. The dyads are different with each Part.

- For Part 2 on Generics ABC there is the *Mythical Interview of Patient (speech in italics) asking the Doctor (speech in plain text)*.
- In Part 3, on financial implications of generics, the *Student is interfacing with the Medical Economist*.
- In Part 4, Knotty Problems the Doctor talks to the *intelligent layperson*.
- In a second paper, Section 2², we will look at more complex areas such as Quality Controls, Narrow Therapeutic Index, generics in different countries, and nutritional supplements, and attain a broader perspective.

By this means I hope to be able to more appropriately target different levels of readership as we progress through different sections, or alternatively to provide a graded education on this topic. Some readers who are not in the health professions may find certain sections more appropriate for them such as this Section 1 paper and the Section 2 on Nutraceuticals.^d

So should I use generic or brand name drugs or nutritional substitutes?

This is not meant to give medical advice to any reader. Every situation is different. The ultimate choice is the patient's, not the physician's.^e But let's develop a perspective.

^c This genre utilizes a major technique of the dialogic style of sciction (see Telicom article 21:2, 77-87, but does not have the fully formed characterizations or composite patients. It is not education through literature here, but education by interview.

^d The challenge here is independent communication in each part as well as unifying them together creating an ongoing educational stream, which remains coherent and comprehensible.

^e The patient or patient advocate may wish to independently review the literature on the specific compounds, knowing it may be difficult, if not impossible to obtain all the pertinent information, with all the pros and cons, and that such interpretations of the literature may be best suited to experts in the area. The patient should nevertheless endeavor to keep the physician current as to any medications and supplements being taken.

The ABCs of Generic Substitution (Part 2)

Vernon M. Neppe

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

Generics delineated and their relevance.

What is a generic drug?^{3 4}

Generic drugs, or *generics*, are approved as equivalent in active ingredients to the *original brand name drug*. The approval agency (e.g. FDA^f) regards both as having ostensibly equal biochemical composition.^g Thus, generics are considered equivalent substitutable products to the brand drugs (e.g. venlafaxine generic; Effexor brand). Generics are not patent protected; brand name drugs usually are initially.

What is the overriding reason to prescribe a generic?

To save money for the consumer, the health care industry and ultimately to save health costs in the country. The generic is cheaper than the branded drug.

Please clarify.

Generics usually cost half or a third or even a tenth of the price of the brand name (branded) drug. This can save both patients and medical insurers billions of dollars annually: Ideally, this saving should be without compromising the quality of care.

But that's provided they do what they're supposed to do?

True. The assumption is they are identical in safety—no greater side-effects—and have equivalent efficacy—they work clinically, and that the same amounts are available using the specific dose and route of administration (such as oral).

*So generics are equal?*ⁱ

In broad terms, actually there are differences—but these are regarded by the regulators as insignificant in clinical practice. So technically, yes, they're equal, but there are times when the exceptions are relevant. The major premise is that these medications are established as so-called *bioequivalent drug products* and they are assumed to be *therapeutically equivalent* and, therefore, interchangeable with the standard—the branded drug. This bioequivalence implies measures of peaks and concentrations correspond between the generic and the brand; the therapeutic equivalence means the drug substance is chemically identical when delivered to the site of action at the same rate and extent as another drug product producing the correct clinical effects. In other words, the generic drugs conform to several strict criteria. This is relative equality as you'll see!

*But is there a way that the generics differ?*³

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

^g http://en.wikipedia.org/wiki/Generic_drug

^h Rarely, the actual formulation is patented.

ⁱ Drug Price Competition and Patent Term Restoration Act of 1984 informally known as the "Hatch-Waxman Act". This standardized the USA procedures for recognition of generic drugs.

Yes. The generic drug has to have its own "concrete" to put it together. We refer to that as its *vehicle*. Part of this vehicle include the other ingredients (*excipients*) that produce the exact formulation. This may explain side-effects such as nausea, which are not found in the original compound but where irritation of the stomach occurs, and they also may be associated with allergy.

Can generic drugs differ in any other way from the original brand name ones?

Yes, they can and at times do. Several differences are acceptable. Their shape can vary. They may be packaged differently and their color and even flavor may not be the same. They may have varying preservatives which at times make their expiration time different. These are all acceptable variations according to the FDA. But, the configuration (dosage form) must be the same, e.g., capsule or tablet.

So what is the overriding reason for the consumer not to use a generic?

When we need to ensure that the drug one is taking is exactly what is prescribed without any question as to the quality being inferior to the original compound.

For example?

In some conditions we actually want exact dosing because of risks: Abnormal firing in the brain (seizures) and abnormal firing in the heart (arrhythmias) are examples. Here even small variations could be dangerous.

Any other times?

Yes. Similarly, in other situations the range between therapeutic and toxic dose of a drug may be small. The classical one is the drug, phenytoin (Dilantin, Epanutin) in epilepsy. At one dose, it's therapeutic. Push up the dose by a sixth and it could be toxic. So if we use rules like the 20% variation in bioavailability that could occur in generics, we could have a disaster.

What about other more chronic life and death situations?

A good question. Would you like to receive a slightly wrong dose in chemotherapy? This means a treatment designed to kill cancer cells may not succeed, or may kill off too much of the regular healthy body cells if the doses were too small or too large.

Do we have a term to describe these critical examples?

Yes. We sometimes want more precise dosing in these drugs: We call them "*narrow therapeutic index*" compounds.

For what diagnoses should I consider such drugs?

Certainly we want to adequately treat acute problems like seizures, heart arrhythmias, asthma attacks, heart attacks, hyperglycemia and pain. All these require more exact onset of action and dosage.

So why should the brand-name drugs be any better in these cases?

Their quality and reliability are generally well established by many years of study and extended clinical experience. Moreover, the generics are based on them as comparisons, so it would be hard to conceive of the generic preparation being "better" though that could theoretically happen.

So here I should use the brand name?

Personally, I may use the brand name drug when dose is critical. I want the dose to be as controlled as I can get in some conditions and in some patients. Ideally, the production of a medication should be so consistent that, if analyzed, we would obtain the same dose every time. But we don't see that often—not even for the branded product.

Are generic drugs sometimes not the same as the name brand? My insurance tells me this is not so.

Generics are generally regarded as equivalent to the original branded drug, but sometimes the quality is so variable that a third category has come about called *Branded Generics*. These brand name generic drugs are still generic in that they are not the original product. However, specific brand names that are cheaper than the original brand are used to facilitate higher quality. An example of a branded generic occurs in hypothyroidism with a specific "generic" thyroxin.

So the newer drugs, like antidepressants, may ultimately be a cost saving?

Yes. The newer antidepressant drugs (still brand name, non-generics) came out not because they were necessarily more efficacious, but because they had less side-effects than the older tricyclic antidepressants (that could be generically substituted)—anticholinergic side-effects like difficulty passing urine, constipation, memory impairment, blurred vision and potentially irregularities in heart rhythm, particularly in high dosage. So newer drugs, like venlafaxine, therefore, could save money, but even more so they could also save lives. But this is not comparing the same generic with the same branded drug.

But are generics then bad?

Not at all. With generics, detailed testing is required and the results are sound statistically. There is also more stringent regulation of manufacture than before. Overall, they do a good job. So, in general, they're not bad, but it's actually complex.

You mean sometimes patients going to the same pharmacy may not even get the same generic each time?

You're right. When the generic is prescribed the patient may get any of many different equivalent generically approved medications. There may easily be twenty or more different preparations for the more popular drugs. You can imagine the cheapest one may end up being dispensed. This may differ from one time to another, which may make the variation even more.

I once was stable on a generic and then suddenly unstable when I used the same prescription again.

This is another problem of generics. You may have received Company A's generic the first time, yet Company B's the second time and the preparations may have varied quite a bit between the two. The pharmacy may dispense differently, and often does depending on the price.

So I should point out to my doctor if it looks different?

Certainly. Also a good pharmacy may write the actual generic brand you are receiving on the label so you can check you are not mixing one you like, with a different one.

But pharmacists cannot change prescribed generics?

But if the doctor prescribes a specific generic, the patient will pay a copay like the brand name.

When do I take generics?

So you recommend generics?

In my opinion, most generics are okay, but I certainly don't globally recommend all. "Narrow therapeutic index" drugs require special care because variations are more critical. Each case must be carefully assessed.

But there are conditions in which one should always use branded drugs?

There is no "always" in medicine. Some medications are safer than others. The most dangerous groups to generically substitute may be those that can produce some kind of fatal effects, either side effects or therapeutic lack of effects. Imagine heart irregularities. You want the best anti-arrhythmics for the heart.

So when could we prescribe generics safely?

When we are applying appropriate common sense. For some conditions, such as depression, the greater variation with generics will not usually make much difference. The variations the FDA has regulated may seem liberal, but they're based on a medical decision that for most drugs, the difference in the concentration of the active ingredient in the blood does not make a significant difference clinically. Moreover, this difference reflects the limit of range, and the detailed statistical criteria that are also required make it unlikely that any drug with the most extreme limits of variation allowed could be approved as equivalent. In fact, not infrequently, the generic drug is from the same company as the original drug and meets the same production standards.

Why would the brand name company produce a generic and compete against themselves?

Because they have lost the patent on funding. It means other companies can copy their drug and although their profit margins may drop considerably, the original company still has the machinery in place to make a smaller profit and compete easily with other generic companies.

When do I not take generics?

Why won't you prescribe generics with epileptic patients?

Not quite. I am more careful with patients who have conditions where loss of control may produce major consequences. So seizures and heart arrhythmias are good examples. But some recent generics are so good in that regard, that I try to be sensible, taking the patient into account, looking at the specific preparation and the costs. In an ideal world, with no cost considerations, I would not substitute the brand name drug.

But for patients with depression, would generics always be okay? ³

Only sometimes. You must consider each case carefully. Some people are very sensitive to small changes in dosage. If so, I would use the same brand name product. On the other hand, if finances are a concern, and the dose the patient takes does not seem critical, then I would use the generic. But I do have a fantasy.

What's that?

I wish I could make sure that the patient would get the same brand of generic each time, but I can't, so the risk is always weighed with the financial benefit. Often the pharmacy will dispense what is most easily available and sometimes that is a cheaper generic and that may have changed. I try to encourage the use of the same generic if the patient is stable.

I need to take a specific generic medication because I can't afford another prescription drug.

That's a good reason.

For example, I was prescribed some Lamictal, but it was just too much, so I was put back onto Dilantin. Both were brand name drugs.

Yes, these drugs are both used for seizure disorders. This reflects another side of it. Even when we're talking brand name drug, the newer medications are often more expensive than the older ones. It's always a dilemma trying to balance the value of the new medications with the old.

But Lamictal has another use too?

Yes. Many drugs have multiple approved indications. Lamictal is sometimes also used in bipolar illness. There the precise dosage may not be as much of an issue so substitution when available is a legitimate option.

Aren't the older drugs obsolete anyway?

Not at all. Many are well researched and work perfectly well. Often these newer medications differ only because of lowered side-effects. If we have good control without side-effects, then the old ones are fine. If we don't, we sometimes need to go in a newer direction to get better control.

How do you choose?

Remember this: A day's hospitalization sometimes costs more than six months' worth of medication. Consequently, it's cost effective going with the newer medication if the newer medication makes a significant difference. And if you need a branded drug for a good reason compared with a generic the ultimate cost saving may be enormous.

But some older drugs are okay?

Indeed, generic Aspirin (acetyl salicylate) is still one of the greatest drugs we have. It is used daily by millions in low dose (e.g. 81mg) to slightly decrease clotting tendencies and hopefully therefore diminish the risk of heart attack. But even that has changed. The vehicle may be coated so as not to irritate the stomach lining.

But I know there are other special exceptions to generics?

Yes. For example, the more recent development of long acting or extended release medications, which come in a large variety of different (sometimes generic) formulations. You cannot subdivide these special release preparations without destroying the formulation.

But there are exceptions?

Rarely: Occasionally, we find a drug such as with Venlafaxine Extended Release, one is able to actually open up the capsule because the same microencapsulated beads occur every time. On the other hand, one of the preparations of carbamazepine, Carbatrol, has three different kinds of beads, immediate release, relatively slow release, and very slow release kinds of beads. Obviously, these could not be opened. Others involve a special patented form of preparation called Oros or other long-acting formulations and with these preparations, one cannot open up these drugs at all and maintain the same preparation. Consequently, even with the parent compound, one has to be careful in terms of looking at extent of absorption.

What about an allergic reaction?

This may another reason why not to use a generic in someone taking a key medication that is not easy to replace. Imagine having an allergic reaction to the only drug in a group that one does well with? That's a tragedy.

And if the patient is allergic to one generic, would they be allergic to the name brand too, and to other generics?

Possibly, though the glue in the drug, the vehicle formulation, may be causing it and be different. Unfortunately, cross allergies could occur. So physicians are unlikely to take the chance for the patient who specifically needs a particular drug.

So what do you do?

It depends. But particularly if that medication is known to cause rashes quite commonly, or if the patient is prone to allergies which may prevent you taking something you really need, my inclination would be to prescribe the brand name, implying the usually purer vehicle and also the experience of good solid mass production.

But I don't mind putting up with a rash.

Allergy can be very serious. A rash may be just the start and allergy may, e.g., manifest with allergic sore throat, fever or mouth ulcers, or arthritis. Even worse, you may have so-called *anaphylaxis* where your chest closes up and you can die because you cannot breath. You should stop the medicine pending urgent discussion with your physician and may require antidotes. Finally, the occurrence of "bone-marrow depression" is extremely rare but can occur.

So if my blood counts change, I'm in real trouble?

Not usually. When we do a blood count, we will, sometimes see a benign drop in, e.g., the white cell count. This most often means very little.

For some drugs like carbamazepine, this drop below normal is not linked with bone marrow depression and doesn't seem to increase the risk of infection. Some drugs like lithium push up the white cell count and many patients on both find their white cell count adjusts itself. Complex, yes. Again, consult your doctor!

So with allergy potential, can I get a generic?

Sometimes. It depends on the drug, your history, the condition, the other drugs and many psychological factors. I need exact dosing in conditions such as yours, and I'm more likely to be guaranteed that with the same consistent, well-established preparation.

Effectively you're saying that the generic issue is complex and needs more detail?

Yes. And I've endeavored to do so elsewhere.

Generic Substitution: Financial implications (Part 3)

Vernon M. Neppe

Mythical Interview: Student. Interfacing with the Medical Economist.

I discuss below two issues impinging on finances and generics, namely costs and patents.

Costs

What is the current financial situation with generics in the USA?

The generic drug industry in the USA was estimated at \$85 billion to \$100 billion annually, even by 1994. The foremost application is cost-savings to the consumer, to managed care and to insurance plans.

Have changes occurred over time?

Yes. By 1989, generics constituted 40% of the prescriptions yet cost only about 10% of the total USA drug bill. This figure has increased considerably.⁴ For example, by 2002, almost 50% of all prescriptions were filled with generic drug products. So we could speculate on the total USA drug bill being relatively less.

Why are generics so much cheaper?

Generic drugs, in general, cost about 30% to 80% of the branded drugs. This is for two reasons: competition and original high costs.

Please elaborate on these. Let's start with the competition?

Because generic drugs are no longer patent-protected, several generics of popular drugs appear. This increased competition amongst generic companies lowers the price. This is particularly relevant not only for the consumer and the uninsured, but for patients in many developing countries who can afford the generic. The rules for many countries are similar to the United States Model that uses proof of bioequivalence as the major factor for approving the new generic drug for marketing.

So when there's no competition, they cost more?

Correct. Generic drugs can start out fairly expensive, particularly during an initial 180 day "moratorium" type period of exclusivity. The price of the generic then decreases as the rate of production increases and as competition pushes down the price.

What about the original high costs of the branded preparation?

Because the original branded drug cost a fortune to bring to market.

How much exactly?

The average cost to brand-name drug companies of discovering and testing a new innovative drug (with a new chemical entity) may be as much as \$800 million.^j

And I assume that figure is very complexly made up?

Yes, it could be. Imagine that say for every marketed drug, 100 may go by the wayside. So sometimes we talk of 200 million dollars for marketing, the rest maybe based on failed research.

^j "The price of innovation: new estimates of drug development cost.

" DiMasi, J.A. et al. Journal of Health Economics 22(2003), 151-185. Accessed 31st of May 2007

So this explains the enormous costs of the drug?

Yes. The company needs to recoup their investment with profit. This is precarious as they are could also exposed to lawsuits, even long after the drug has become generic. Hence, we should respect these original manufacturers as they are making major advances in medical pharmaceutical care.

What would happen without them?

Without them, we would be practicing medicine in the Middle Ages, unless world governments' took over research and development. But the chance that this happens in the USA, for example, is very small: The Private Pharmaceutical sector funds the overwhelming proportion of drug research compared with, e.g., the National Institute of Health or other private or unfunded research.

And what about medical education?

The pharmaceutical industry, has certainly, until recently, funded the great majority of post-graduate medical education. But changes have happened recently. Their sponsorship is diminishing as Medical Associations have increased their demands for objectivity. In the USA, this has generally led to changes in Continuing Medical Education (CME) where the sponsoring Pharmaceutical Company can no longer choose the speaker for lectures. Moreover, non-CME lectures to colleagues require "fair balance" using approved mandated slide sets.

So how would you rank the interpretations of physicians today versus 10 years ago?

I believe the audience and readership of physicians can now more objectively interpret data. Moreover, speakers possibly deliver more balanced lectures.

So does this mean we have achieved the correct balance in the USA?

No: I think there is still room for more change. In fact, I speculate that the correcting pendulum may currently have overcompensated. However, direct advertising to patients has increased tremendously: this has created new problems.

And what about outside the USA?

I understand the problem may be a growing one in the rest of the world where physicians must be on their guard because of the subtle pressures.^k

You said, "until recently"?

Yes. Changes by regulating agencies, sometimes the companies themselves, have compromised this funding.

It will be interesting to see whether American Medical education will suffer as a result. I think it will considerably.

But then, is there a reason to use branded drugs to support the pharmaceutical industry?

This can be debated in theory:

If I write a book, or invent something, I may receive royalties for tens of years. Yet the patent life of an active drug is so short.

Hundreds of millions of dollars need to be recouped by the original brand-name drug company in what may be only ten years or even less.

Is that fair for a generic company to spend a tiny amount and take over?

^k Professor Mark A. Gillman, South Africa, direct personal communication.

Do the generic companies also benefit indirectly from the marketing of the original brand name company?

Certainly. Previous marketing efforts by the brand-name drug company (media advertising, presentation, educational lectures, free sample distribution and knowledge by physicians and patients of the drug) allow generic manufacturers enormous advantages and the drug is often still referred to under its brand-name even when the generic is received.

I understand the economics you've mentioned. But why can branded drugs cost more?

One reason they cost so much is that they are still patented—there are no generics available. This means there's no competition and makes them more expensive. This cost issue is relevant. Many patients at times abandon their medication because they cannot afford trade (brand) name drugs.

What about really old drugs? Are they automatically generic?

Yes. There's little incentive financially to make a branded drug because the patent has long expired. They're unusual however because of limited previous regulation. For example, the drug phenobarbital in epilepsy has been around for so long that it does not fit the regulatory tests as those only have been available since 1938.

And it would be hard to locate a branded version of phenobarbital.

True. Drugs like phenobarbital in epilepsy are cheap—that's partly because they're old and easy to manufacture. They are generic, and its branded name not really used. But phenobarbital is at the bottom of the rung.

So should such a drug be used at all?

Possibly seldom in Western countries, because economics cannot easily justify the sacrifice of functionality. Yet, because it is so cheap, it is overall the most used anticonvulsant agent in the world.

Patents

When do generics appear?

They are developed only once the patent life protection of the original developer has expired. The time for the generic to be initially marketed varies.

How long do the drug patents last?

Drug patents in the USA allow protection for twenty years. Patents are typically issued on novel pharmacological compounds early in the drug development process. This begins the 'clock' to patent expiration. However, preclinical and clinical research may take eight to thirteen years, sometimes longer. This means the effective patent life of a drug is generally seven to twelve years, but occasionally, new indications or metabolites allow slight extensions.

Is there a minimum patent period?

Yes. The minimum exclusivity patent time of a clinically approved drug is now five years in the USA.

Is this the same outside the USA?

Exact patent life differs from country to country.

What, then, constitutes a new patent?

Patents are more than just new drug development. Interpretations of new versions of the drug vary. Effectively, significant changes to the compound create potentially new patents after new clinical trials.

Would you please list examples?

Examples vary: long acting versions, e.g., venlafaxine (Effexor) versus venlafaxine XR (Effexor XR); different compounding of salts making side-effects less, e.g., valproic acid (Depakene) versus valproate (Depakote); and single enantiomers of drugs (levo- and dextro-rotatory forms), e.g., citalopram (Celexa) and escitalopram (Lexapro).

So is that a new lease of life?

Not quite. The company needs to balance the value of that new patent on the modified compound. This is so even if it may allow an entirely new patent of 20 years, or alternatively a partial patent extension.

Why?

Because it does not prevent sales of the generic versions of the original drug. This means the drug may be a bust because the cheaper generic alternatives will be bought. And sometimes such a patent runs into troubles.

How so?

Litigation may occur by the generic companies, e.g., with buspirone (BuSpar) when the company apparently could not defend an extension of patent application when it was challenged. At a minimum, the original company needs to recoup its costs.

Please briefly clarify the patent expiration issue?

Generic drugs can be legally manufactured after the patent has expired or when the generic company certifies the brand company's patents are either invalid, unenforceable, or will not be infringed. Of course, when the drugs have never held patents (some vitamins are like this) or in countries where patents are not enforced we can see generics immediately. Some compounds have so-called *USA patents*, others *world-wide*, but some countries, anyway, apparently ignore patents.

How does one extend patents on drugs?

Critics talk about "*evergreening*." This refers to attempts at maintained market exclusivity on brand-name drugs and prevention of generic competition. Billions of dollars may be at stake—imagine sales of \$400 million per year for another ten years! Litigation to preserve or extend patent protection on branded drugs is not uncommon.

What about other pharmaceutical brand company extensions?

Sometimes companies license a subsidiary company to sell generics under the original patent (*authorized generics*), and they then remain under the original patent holder's drug application.¹

Do the initial generic companies have rights too?

¹ With simvastatin (Zocor), Merck apparently lost its US patent protection on June 23, 2006. Ranbaxy in India and Teva in Israel each received 180 day exclusivity periods for simvastatin and began marketing their products immediately after the patent expired.

Yes. In the USA, the FDA may grant a 180 day exclusivity period to generic drug manufacturers. This is so in contested patent cases and relates to the generic manufacturer being willing to risk the extensive costs of patent court litigation. This way, the generic manufacturer need not produce the drug during this period, yet can prevent other generic producers from selling the drug.

When does the generic become available?

Once the patent life expires, if the drug is popular, generic drug manufacturers frequently rush to produce generics. In some instances, there may be 20 or 30 different generic compounds; in other instances, only a single compound.

What about the original company?

The compound could even come from the parent pharmaceutical company but be produced and marketed by another company, without the public knowing. In other words, one is receiving the actual brand, but in the generic name, sometimes at a fraction of the cost. At times, when there is very little competition, the cost may still be 50% or 60% of the original; at other times, it might be some 10%. Consequently, there is enormous cost savings to the use of generic substances.

Surely, Doctor, the newer drugs are better than the older ones? Hence we should appreciate patented drugs?

Yes and no. The newer drugs are often better, but we should be cognizant that besides being more expensive, they have their own side-effects as well. Moreover, we don't have thirty years of experience with them.

So how does one balance the economics?

You should always understand there are not only direct costs of a medication, but indirect savings sometimes: A day saved from hospitalization may allow a year's prescription of drugs. A real issue is, therefore, whether or not patients will be hospitalized. Or if they were in the hospital, will it even be one day less? The costs incurred by one day of hospital stay may be equivalent to approximately six months of treatment as an outpatient on the new drug. Consequently, any minor subtle change which increases the quality of the patient's life is of enormous relevance. It's not only an issue of hospitalization, but of functionality. If somebody is able to be third, as opposed to 780th, in his company because he's taking one of these newer drugs, can we measure this in terms of cost? Probably not.

And outpatient visits also change?

If these drugs cause more problems, they will increase the number of side effects and the therapeutic potential of the drug. This will increase the number of doctor visits, sometimes significantly, besides increasing the days of hospitalization.

So someone has to carefully consider that balance?

Indeed. On the other hand, the medical insurance industry in the United States might charge 5 to 20 dollars for a generic, and may on the other hand, charge 25 through 80 dollars for the brand name, particularly if the generic is available. This puts the patient under significant pressure to receive the generic, even if they were receiving a brand name prior to the drug being generically substituted because they may now be paying double. However, it does not necessarily imply that one generic is ultimately economically more desirable than the brand name because it is cheaper.

So the politics of generics and maintained patents for brand name drugs clearly have a major impact on the area of generic substitution?

Clearly.

The Nitty-gritty and Knotty Problems of Generic Production (Part 4)

Vernon M. Neppe

Mythical Interview: Intelligent Layperson. Interfacing with the Doctor.

Production and quality

Does one always see generics being used with popular drugs?

Usually, but not always. For example, Coumadin (warfarin) is an anti-coagulant. It has such a narrow dosing window requiring frequent blood tests to ensure appropriate bleeding tendency. Many physicians would not generically substitute, even though an Ontario study showed the generic safe. Therefore, there has been, till recently, limited generic use⁵, but this is now changing.

And in some instances, I would assume that some drugs are actually not as safe?

Maybe. There is another Canadian study on lamotrigine (Lamictal), an anticonvulsant, where costs increased when the generic was given,⁶ despite the two formulations being demonstrated independently to be identical.⁶

Once generics are produced, do we ever see improved quality?

Sometimes. But then it is used as a new brand name drug e.g., carbamazepine is now produced as Carbatrol, or some newer long-acting Ritalin preparations.

But don't the many generic drugs in one brand also create inferior products?

To the extent that the FDA has approved the generics as equal, no.

But to the extent that the vehicle in the drug may vary, yes. In reality, the vehicle that glues the drug is not as well regulated. Bioequivalence provides only that the drug after absorption is statistically equivalent. But we may see very different formulations appearing. This is one reason why a patient receiving one generic, then changed to another, may experience side-effects, or even worse, allergic reactions, possibly to the vehicle. This can be particularly compromising.

What criteria exist for controlling the quality of a generic?

We know that generics must contain approximately the "same" dose of the equivalent active ingredient. Also, they should be of similar quality and purity. They must produce the same effects on the body and be as safe as the original brand name product. This is why, in practice, generics usually work like the original brand name products, and they save a great deal of money because they're much cheaper.

You said the "same" dose. Who polices the "same" dosage idea?

The FDA.¹ They have strict controlling regulations to try to ensure that the chemical parts of the drug that are relevant are equivalent. Generic drugs must, of course, be produced using acceptable standards of control. Although, technically, there may be quite a wide variation, a drug which was just in the acceptable range would probably not last long in the marketplace or be marketed at all. Most generics are not too bad. In fact, they're reasonable replicas of the original at a fraction of the cost.

You mentioned the "same" dosage. What's the range the FDA allows?

The technical term used is bioavailability. This must be deemed the same by experts: Technically, the active generic drug must be absorbed and become available in the relevant organ (such as the brain with neuropsychiatric medications) at a speed and degree comparable to the original standard brand name drug.

But what's the "same"? I want to understand this.

Bioavailability is a complicated concept; simplifying it may make you interpret it incorrectly.³

Well, what's the bottom line?

Superficially, the FDA criteria may seem rather liberal for generics.

Figures exist for what's equivalent. Technically, the peak blood levels and amount of drug in the blood over time could vary by 20% less or 25% more to be generally considered "bioequivalent". This is called the -20%/+25% rule.

So does this compromise the generic drug?

There could be compromises in the use of generics in several circumstances. How bioequivalent are these drugs with this 80-125 rule? It is rather shocking for most when first heard because conceivably 100 milligrams of a brand name drug may be equivalent to say between 90mg or 110 milligrams of the generic. This may not cause major problems for most drugs, but for those drugs with narrow therapeutic indices, the variance of a specific dosage to produce their effects maximally without side effects, sometimes extremely toxic, could not only be dangerous but potentially fatal.

It does seem to be a big difference, doesn't it?

Yes. It may be, but we have to have some cut-off range. Usually, this wide range is considered okay.

But...

Yes, there is a but... But you can imagine that's why I don't like generics in critical situations. With antiseizure medications, for example, this is why I don't want my patients to receive 550 mg of carbamazepine when they should be getting 600 mg. The risk of seizure is too high. Similarly, I think people with potentials towards irregular heartbeat may be impaired if the drugs that normalize their heart rhythms were off by such a range. Alternatively, some drugs have a small range between therapeutic and toxic dose as with Dilantin where a person who was under control becomes toxic—confused, sleepy and unsteady on his feet—when a minor dose change occurs. Even worse, he may start to seize because the brain levels are too high. Generic variations, therefore, may cause problems in this kind of patient.

But Doctor, why is the FDA not imposing a 100% equivalence on drugs, instead of an 80% equivalence?

At a certain point, we have to be reasonable in setting standards, and this approach allows for variations. There are variations even in the parent compound, which means that if we had close to 100% equivalence on generics, what would we compare it to?

So the parent compound itself might still fluctuate a little bit?

Yes! And the -20/+25 rule recognizes that this degree of variation, in most conditions, will not be harmful to most patients. In reality, the range of acceptability works out narrower than this, and there are fewer variations. Most commonly, today's generic drugs fit a -5%/+5% profile. Specific rules guide individual drugs with the ultimate responsibility involving the manufacturer, not the FDA.

I still don't understand fully.

The 80-125 rule is not as easy as it looks. First of all, why the figure 125 on the one side, not 120? Simply because for 80 over 100, it's reciprocal would be 100 over 80, which is 125%. However, it's not as easy as it looks because this really relates to certain complex features, such as area under the curve and maximum kinds of concentration being distributed within these boundaries within 90% of cases.

So that's not so bad?

Correct. Very often the mean of the data is usually close to 100% of the test reference drug. These figures were ascertained because expert pharmacologists decided these were appropriate equivalents. Therefore, they may also fail if the variability of the original product—the brand name drug—being tested was high.

And what about different people?

Very astute: Yes, it's also dependent on the normal volunteer who may reflect wide patient variability of these parameters—some drugs vary enormously depending on genetic factors. Therefore, the reference product is also variable.

Do you have actual figures?

Yes. But I'll be technical here. Don't worry if these terms are not comprehensible, it's the principle that counts.

Do tell!

The Office of Generic Drugs has found that in 224 bioequivalent studies submitted in approved applications from 1985 to 1986, the observed average differences in the area under the curve was 3.5%, and the standard deviation was only 2.84. For Cmax, it was 4.29%. The current practice carries out two one-sided tests at the 0.05 level of significance.⁷

And in English?

This ensures that there is no more than a 5% chance of a generic product that is not truly equivalent to a reference product being approved.⁷

So this sounds okay! But is it worse than this?

Possibly. There is a further component here, and it is that the 80-125 rule needs to apply in only about 90% of the compounds that are tested. This means that if one tests a batch of 100 drugs, if 90 comply, that is ok. But what about the remaining 10? These are extreme situations and just parts of rules that are not necessarily relevant because one is generally dealing with a far narrower range.

But in the real world, are these extremes so?

Not too much: Although we talk about the 80-125 rule, realistically, most of these generic drugs are very close approximations of the original compound. In other words, it might be 95 to 105 milligrams in a significant proportion of instances.

But there are several generics?

Exactly, there are numerous different generic compounds at times for the same brand name, which means that there still may be enormous variability between them.

So this is one of the risks of using many generics in the same patient?

Yes. The generic compound may be substituted to a different generic and the patient may not even know. The one time the patient may indeed be receiving 120 milligrams of it, and another time 80 milligrams potentially. I've even seen a situation where the patient after receiving the same generic for years, destabilized because she was given the brand name drug instead. This may have related to her receiving 100 mcgs of the same generic thyroid hormone for years and her then receiving the "same dose" of the brand name drug. This made her thyroid overactive because the generic was actually equivalent to 90 mcgs and the brand to 100 mcgs of the real chemical. The 10 mcg/day difference caused destabilization.

What about the parent compound, the original branded drug? How perfect are those?

Well, again, there are rules, and the rules are far more restrictive because of higher levels of quality control. After all they required the clinical studies of efficacy and they have, also, demonstrated experience for many years.

So the brands are good?

Not always. There can be problems. There is also potential variability amongst these drugs, although far, far less because the degree of control has been far, far more.

Similar preparations and sensitivity

I know some drugs have various choices, like different preparations? What preparations should I take of my Tegretol, as an example?

True. For example, Tegretol comes in several slightly different preparations—the regular 200 mg tablet, different longer acting versions (Tegretol XR and Carbatrol), a chewable preparation, and even a liquid. You must be careful to just substitute the one kind for the other, as they may not be exactly equivalent like a generic would be for its exact brand name counterpart.

Why are these all so different?

Let's use as an example a chewable preparation: If truly chewed, it is better absorbed; even more so, a sublingual preparation of, e.g., vitamin B12 may avoid part of the stomach and get absorbed better. Similarly, long-acting preparations may be absorbed but at lesser rates; or liquids may be highly absorbed, but it will depend on what's in your stomach. So each might be a little different, depending on absorption. This important principle can be applied with many different medications.

Is the liquid for a really low dose?

Usually they're made for children and the elderly. But yes. We can use liquids when we want very low dosing. A few people are exquisitely sensitive and need the tiny amounts that can only be dispensed in liquid form. Higher doses knock these medication non-tolerators out. So if you're experiencing side-effects on the low starting dose, I don't want you to decide, "*I better not take it, I must be allergic to it.*" You're not allergic to it: It's just that you're taking too much, like taking twelve aspirins when you only need one. There's an advantage to being so sensitive because it keeps your medical bill down!

And here is an example where we may want to use the brand name preparation because exact dose would be an issue?

Exactly.

Generic Substitution or Brand Drug: An Interim Perspective

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. We will be able to understand more when we examine these in greater detail later?

But for the moment, what do I do? Branded drug...when?

Let's say we want to be particularly careful when the patient has a potential life-threatening acute condition, in certain kinds of drug allergies, and when the medication has a low range between therapeutic and toxic doses: In those situations, we certainly may consider the brand name drug.

So I can look forward to understanding this more?

Indeed, stand by for Section 2! ^{2, m}

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^m Both Sections 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.