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INSTRUCTIONS

1. After carefully reading this lesson, study each question and select the one answer you believe to be correct. For immediate results answer online at www.Canadian HealthcareNetwork.ca.

2. To pass this lesson, a grade of at least 70% (11 out of 15) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies). (Note: some provinces require individual technicians to notify them.)

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Understanding bioequivalence of generic drug products in Canada

by Brandon Tenebaum, BScPhm

Learning objectives

After studying this lesson, the pharmacy technician will be able to do the following:

1. Gain an understanding of trends in Canadian healthcare spending and the role generic drugs play in that system
2. Understand the extent of cost-related nonadherence to prescription drug regimens in Canada
3. Gain an understanding of the assessment of bioequivalence of generic drug products in Canada
4. Appreciate the role pharmacy technicians can play in explaining to patients the similarities and differences between generic and brand name drugs

Introduction

In pharmacies across Canada, both brand name and generic drugs are dispensed. The brand name drug, also known as the innovator or reference drug, is initially marketed as a new chemical entity. Patents for pharmaceuticals last for 20 years following the initial patent filing under the terms of the World Trade Organization's Trade Related Aspects of Intellectual Property Rights

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(TRIPS) agreement. The length of this patent protection may be extended pending the outcome of negotiations between Canada and Europe in the Comprehensive Economic and Trade Agreement (CETA).[1] Once patent protection expires, a copy (i.e., a generic version) of the brand name drug can be marketed.

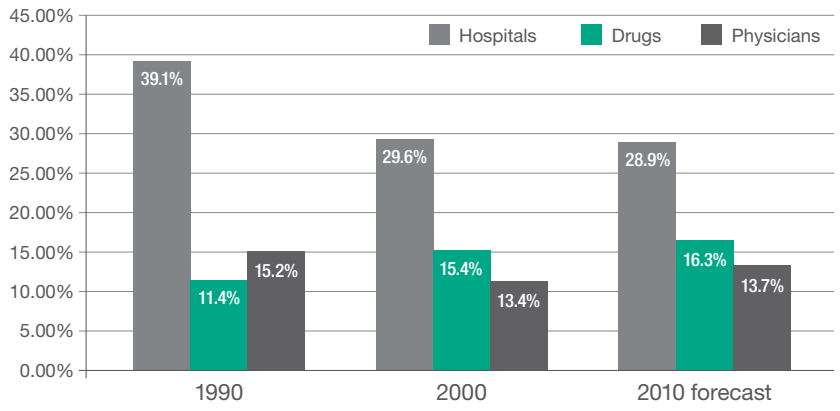
Generic drugs offer a lower-cost alternative to patients and payers, as generic producers spend less on research to make copies of the brand name drug. In addition, competition is introduced into the market, helping to drive prices down. This is important, as it was forecast that Canadians would spend an average of $955 per person per year on pharmaceuticals in 2014. It was projected that total drug spending will be the second largest category of health expenditure in Canada, with prescribed drugs representing 13.4% of total health expenditures in 2014.[2] Recent estimates indicate that nearly 45% of all prescriptions filled by pharmacies use generic drugs.[3] As payers seek to contain rising healthcare costs, increasing use of generic drugs is one strategy being used to achieve this goal.

Canadian trends in pharmaceutical spending

A 2012 report by the Canadian Institute for Health Information highlighted the fact that pharmaceuticals have been one of the fastest growing components of health spending in Canada over the past two decades. As indicated in Figure 1, since 1997 drug expenditures have ranked second only to hospital expenditures with respect to their share of total healthcare spending in Canada.[4] Between 1998 and 2007, retail spending on prescription drugs outside of hospitals grew at an annual average rate of 10.1%, according to IMS Brogan's Second Generation Canadian CompuScript Audit.[5] Some of the factors and their average annual contribution to this growth rate include the following:

- Population growth (an average annual 1% contribution to prescription drug spending)
- General inflation (2.6% contribution)
- Population aging (1% contribution)
- Volume effects, which include the number of people taking prescriptions and the quantities of those prescriptions (6.2% contribution)
- Starting or switching to a higher-cost drug within a drug class (2% contribution)
- Price effects net of general inflation contributed to a 2.7% decrease in drug spending

FIGURE 1 - Selected category breakdown of total health spending, Canada, 1990 to 2010



Sourced from National Health Expenditure Database, 2011, Canadian Institute for Health Information.[6]

The effect of generic drugs on Canadian pharmaceutical spending

The entry of new generic drugs helped to more than offset the effect of inflation on drug costs for the period between 1998 and 2007. Price effects contributed to an average annual 2.7% decrease in drug spending net of general inflation, which was 2.6% annually for the same period. Price effects account for changes in drug price and moves in usage between brand and generic versions of a particular drug.

Cost-related nonadherence

For patients without adequate insurance coverage, the cost of medications can present a barrier to medication therapy adherence. Based on the 2007 Canada Community Health Survey, 9.6% or about 1 in 10 Canadians who received a prescription reported cost-related nonadherence.[7] As high drug costs are a barrier to adherence, having more affordable generic versions of a drug available may help to eliminate this barrier.

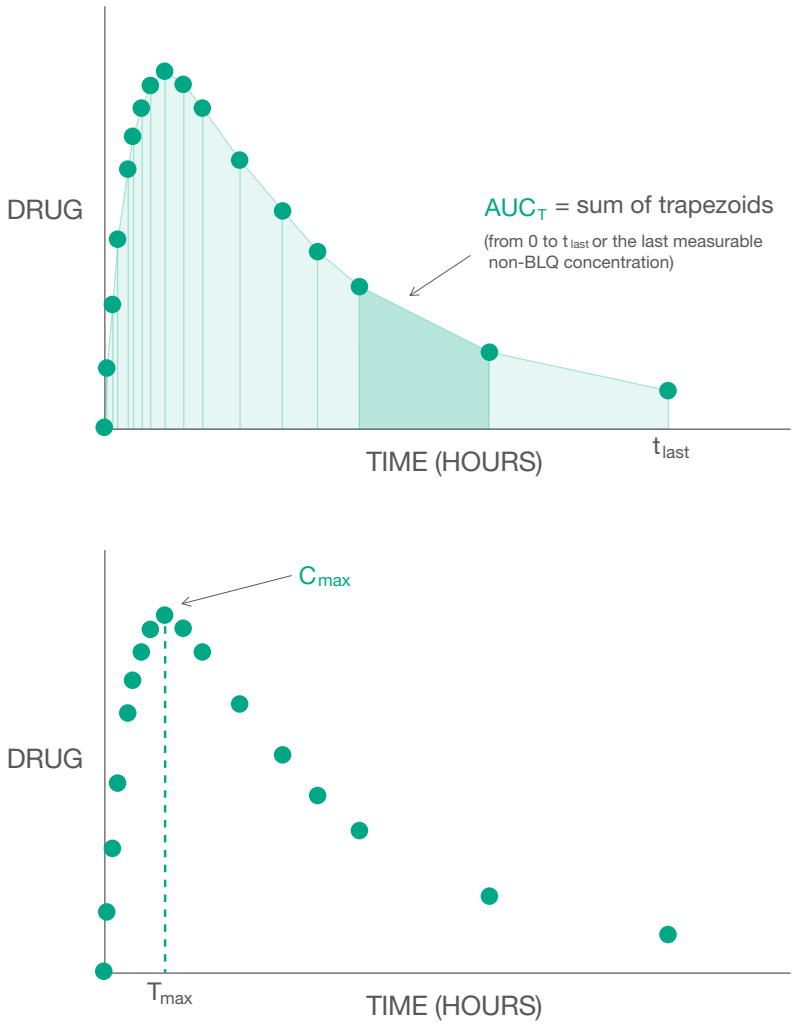
Similarities between generic and brand name drugs

The brand name drug and the generic version contain the same active ingredient within the same potency tolerances as the innovator product (±5% of potency label claim) and have the same mechanism of action in the body.[8] Generic drugs are considered bioequivalent to the reference product. *Bioequivalence* is a term that will be explained in more detail in a later section of this lesson. In addition, federal guidelines for Health Canada's good manufacturing practices must be met for both brand and generic drugs with respect to manufacturing processes, facilities and ingredients. All drugs sold in Canada must be reviewed and approved first by Health Canada. Health Canada also has the authority to remove or quarantine generic or brand name products from the market if it is made aware of any deficiencies in good manufacturing practices.

Differences between generic and brand name drugs

Generic drugs offer lower-cost versions of the brand name drug. Although they have the same active ingredient, the inactive ingredients (excipients) such as diluents, preservatives and flavours often differ between generic and brand name drugs. In light of these potential differences, the generic manufacturer must provide studies showing that any changes in nonmedicinal ingredients between the brand name drug and its generic counterpart have not substantially altered the bioavailability. Product shape, markings or colour of the generic product may differ from those of the brand name drug. While these differences in appearance may be believed to affect patient adherence, one study looking at

FIGURE 2 - Simulated graph of drug concentration versus time



AUC—area under the curve; BLQ—below the limit of quantiation; C_{max}—maximal plasma concentration.

generic substitution of antidiabetic drugs showed that adherence was not negatively affected by these factors.[9] Packaging and container design can also differ between generic and brand name drugs. The differences in container design can be significant, as one study found differences in the viscosity and bottle design of one glaucoma medication resulted in the delivery of significantly different drop volumes when comparing the brand and generic versions.[10]

Bioequivalence of generics

Generic drugs are required to meet Health Canada's standards for bioequivalence. Bioequivalent drugs have comparable bioavailabilities. Bioavailability is a measure of the rate and extent of absorption of the active drug (i.e., the amount of drug) reaching the systemic circulation system (blood/plasma). Based on the assumption that bioequivalent drugs produce the same therapeutic effect, new safety and efficacy studies for generic drugs are generally not required by Health Canada.

Generic drugs undergo comparative bioavailability studies that measure the level of active ingredient in the blood of healthy human subjects. Typically, the study subjects receive both the brand and generic drugs on separate occasions, so that a comparison of blood drug levels can be made. Although suitable for oral drugs, comparative bioavailability studies may not be appropriate for some medications such as topical ointments or creams. These products may be subject to other methods of testing, such as clinical efficacy studies.

Maximal plasma concentration and bioequivalence

A very important assessment for bioequivalence is the maximal plasma concentration (C_{max}). The C_{max} is the highest measured concentration of drug in the blood or plasma (Figure 2). In Canada, the relative mean C_{max} for a clinical trial must be within the Health Canada–defined limits of 80% to 125%. This means that for a bioequivalence trial of 12 subjects, the average C_{max} of the generic product should be no less than 80% and no more than 125% of the innovator product. C_{max} is a parameter associated with safety; a C_{max} that is too high may be associated with adverse events, whereas a C_{max} that is too low may be associated with a lack of therapeutic efficacy.

Area under the curve and bioequivalence

One important measurable factor used to assess bioequivalence is the "area under the curve" (AUC). The AUC, which correlates well with the body's total drug exposure, is based on a graph of drug concentration in the blood or plasma over time, as illustrated in Figure 2.

The 90% confidence interval of the test/reference ratio for the AUC of the study population should be completely contained within the Health Canada–defined bioequivalence limits of 80% to 125%. This means that there is less than a 5% probability that the true average AUC of the generic drug product is not within 80% to 125% of the reference product.[11]

The 90% confidence interval provides a range within which we are 90% confident that the mean measurements lie. In other words, of 100 bioequivalence trials, 90 of them would be expected to have an average AUC of the generic within 80% to 125% of the innovator AUC.

This has often been misinterpreted as meaning the generic drug concentration can range from 80% to 125% of the brand name version (i.e., a variance of up to 45%). However, this actually means that for the entire confidence interval to lie within the 80% to 125% range, the variance is generally less than 5%.[12]

Statistical interpretation of the AUC confidence interval

Based on international consensus that differences of less than 20% between the AUC and C_{max} of brand name drugs compared with their generic equivalents are not clinically significant, the ratio of generic to brand drugs for each pharmacokinetic variable (AUC and C_{max}) will not differ by more than 8:10. Therefore, the lower limit of 80% is defined by the ratio of 8/10 = 0.8, and the upper limit of 125% is defined as the ratio of 10/8 = 1.25.

Additionally, the 90% confidence interval of the AUC must also lie within the 80% to 125% range.

Bioequivalence with critical dose drugs

For drugs in Canada that have been designated as critical dose drugs, such as warfarin and digoxin, there are more stringent guidelines for establishing bioequivalence.[13] This is because these drugs can be highly toxic or have narrow therapeutic ranges (i.e., the concentration of drug at which the patient will experience the desired clinical effect with a minimum of undesirable or adverse reactions). The requirements for bioequivalence in critical dose drugs include the following:

- Studies must be done in both fasting and fed states, whereas normally only the fasting state is required.
- The 90% confidence interval for the C_{max} should be contained within the limits of 80% to 125%, whereas normally only the relative mean C_{max} is required.
- Tighter confidence limits of 90.0% to 112.0% are used for the AUC ratio.
- Steady-state studies are not required for critical dose drugs unless warranted by exceptional circumstances. If a steady-state study is required, the 90% confidence interval of the relative mean C_{min} (minimal plasma concentration) of the test to reference formulation should also be between 80.0% and 125.0% inclusive.[13]

The role of the pharmacy technician

Patients will often question whether there are differences between brand name drugs and their generic equivalents. The pharmacy technician is in an ideal position to address some of these concerns. It is important to be able to explain the standards set out for

drug approval by Health Canada, the standards for bioequivalence, and the role that generics play in the healthcare system.

Technicians can also help patients to understand their insurance coverage and how generic drugs fit into that plan.

Pharmacy technicians can explain the similarities and differences between brand name drugs and their generic equivalents, and how both play a role in maintaining patient health.

An opportunity exists for collaboration between pharmacists and pharmacy technicians, as they should work together to develop a consistent and easy-to-understand communication strategy surrounding generic drugs and their bioequivalence with brand name versions.

Pharmacy technicians can play a critical role in alerting the pharmacist of any changes in type of drug prescribed so that the pharmacist can have a meaningful dialogue with the patient regarding any differences in appearance of their medication.

By being knowledgeable in this area and being able to communicate effectively with patients on the topic, pharmacy technicians can free pharmacists' time to engage in core and expanded scope services.

Most importantly, the pharmacy technician can augment pharmacists' efforts by stressing the importance of adherence to medication regimens with brand or generic drugs in order to reach therapeutic goals.

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QUESTIONS

Please select the best answer for each question and answer online at www.CanadianHealthcareNetwork.ca for instant results.

1. Currently, in Canada, patent protection for pharmaceuticals lasts for

a) 10 years b) 15 years
c) 20 years d) 25 years

2. Between 1998 and 2007, retail spending in Canada on prescription drugs outside of hospitals grew at an annual average rate of

a) 5.1% b) 6.3%
c) 10.1% d) 12.1%

3. Between 1998 and 2007 in Canada, which factor contributed the most to average annual increase in retail spending on prescription drugs outside of hospitals?

a) An aging population
b) Volume effects
c) Population growth
d) General inflation

4. Choose the answer that best describes the order of health spending as a share of total health spending in Canada from lowest to highest in 2010:

a) Physicians, hospitals, drugs
b) Hospitals, physicians, drugs
c) Drugs, physicians, hospitals
d) Physicians, drugs, hospitals

5. Based on 2007 data, which answer best describes how many Canadians reported cost-related prescription nonadherence?

a) 1 in 6 Canadians
b) 1 in 7 Canadians
c) 1 in 10 Canadians
d) 1 in 12 Canadians

6. A patient calls complaining that her pills do not look the same as before. Choose the best response:

a) Tell the patient not to worry, as the generic version can sometimes look different but has the same active ingredient
b) Tell the patient to immediately stop taking the medication and see the doctor
c) Tell the patient to bring the pills to the pharmacy for a visual inspection. After confirming that they are the correct pills in the generic version, tell the patient not to worry and send the patient home with the pills
d) Tell the patient to bring the pills to the pharmacy for a visual inspection. After confirming that they are the correct pills in the generic version, you tell the patient that while the generic version of the pills look different, they contain the same active ingredient as the brand name drug. You also tell the patient not to hesitate to call with any similar concerns in the future

7. A patient makes a statement that generics are of inferior quality compared with the brand name version. Choose the best response:

a) There are no differences between the brand and generic versions
b) Generics save on manufacturing costs and this is reflected in the price
c) Generics help to save patients money
d) Federal guidelines for good manufacturing practices must be met for both brand and generic drugs with respect to manufacturing processes, facilities and ingredients, and all drugs sold in Canada must be reviewed and approved by Health Canada

8. A patient asks, “How do we know that the inactive ingredients will not affect the safety or efficacy of the generic drug?” Choose the best response:

a) The ingredients are inactive, so that they will have no effect on how the drug works
b) The brand and generic drug have exactly the same inactive ingredients
c) The generic manufacturer must provide studies that any differences in nonmedicinal ingredients have not altered the bioavailability (or rate and extent of absorption) of the drug
d) It is only important that the active ingredients are the same

9. A doctor calls in angry that the pharmacy switched her patient’s drug to the generic version. Upon checking, you see that the doctor did not write “no substitutions” on the script, and legislation in your province requires that the lowest-cost interchangeable drug be dispensed. Choose the best response:

a) Tell the doctor that the brand and generic version are the same and there is no need to worry
b) Tell the doctor that you will switch the drug to the brand name version immediately
c) Tell the doctor that the pharmacy is required to dispense the generic version.
d) Tell the doctor that while the brand and generic version of the drug are interchangeable (i.e., bioequivalent) and provincial legislation requires the dispensing of the lowest-cost interchangeable drug, the pharmacy can dispense the brand name version if the doctor writes "no substitution" on the prescription. However, the patient may be required to pay extra for the brand name version, depending on their insurance (if any)

10. A patient complains that the cost of his medication has become unmanageable. You see that the patient has been receiving the brand name version of a drug when a lower-cost generic version exists because the doctor has indicated “no substitutions” on the script. Choose the best response:

a) Tell the patient the pharmacy will immediately switch the medication to a lower-cost generic version
b) Tell the patient he has to get the more expensive version of the drug because his doctor wrote “no substitutions” on the prescription
c) Tell the patient he needs to talk to his doctor about getting less expensive medication
d) Tell the patient that a lower-cost, interchangeable, generic version of the drug exists, but the brand drug was dispensed because his doctor wrote “no substitutions” on his prescription. If the patient wants to switch to the lower-cost generic version, he can speak directly with the doctor or the pharmacy can contact the doctor on his behalf.

11. A patient has heard that the drug concentration of generics can vary between 80% to 125% of the brand name version. Choose the best response:

a) Tell the patient that these differences do not affect the efficacy of the drug
b) The patient should be corrected that the drug concentration of generics can vary more or less widely than 80% to 125% in a single person. The limits of 80% to 125% represent the allowable limits of the average result of a population in a clinical study. However, these differences have not been shown to affect how well the drug works, and there are narrower limits (90% to 112%) for drugs with particular safety concerns
c) Tell the patient that this difference only matters for drugs with a narrow therapeutic index
d) Tell the patient that this range is acceptable by international consensus

12. A patient who takes warfarin is worried because it is a potentially dangerous drug and small differences with the generic version compared with the brand name version may be harmful. Choose the best response:

a) Tell the patient there are no differences between the generic and brand versions of warfarin
b) Tell the patient all generic drugs undergo the same rigorous testing before approval
c) Tell the patient that this type of drug has stricter criteria for determining equivalence to the brand name product and undergoes more testing for safety. Her doctor will be checking the concentrations of warfarin in her blood and adjusting the dose of the formulation she is given. For other drugs in Canada that, like warfarin, have also been designated as critical dose drugs, there are more stringent guidelines for establishing bioequivalence
d) Tell the patient that she will be monitored by her doctor for any harmful effects

13. A patient wants to know how the generic version of the cream he is getting was tested. Choose the best response:

a) Patient blood level concentrations after applying the generic version were measured and compared with those of the brand version to ensure they were comparable.
b) Some medications such as ointments or creams may not be suitable for the comparative bioavailability studies used with oral medications, and may be subject to other methods of testing such as clinical effect studies. However, topical drugs such as creams present low risk and no additional studies are needed for the generic versions
c) Tell the patient that topical drugs such as creams present low risk and no additional studies are needed for the generic versions
d) Tell the patient the area under the curve (AUC) of the generic version falls between 80% and 125% of the brand formulation

14. A patient asks how it is known whether a generic drug works as well as the brand version if the generic versions do not undergo clinical effect studies. Choose the best answer:

a) Tell the patient there is international consensus that generic drugs work as well as their brand name counterparts
b) Tell the patient Health Canada must approve all drugs before they are sold in Canada
c) Tell the patient the generic drug has the same active ingredient as the brand version
d) Tell the patient that Health Canada ensures that the rate and extent of active drug that reaches blood to exert its therapeutic action is comparable to that of the brand name version, and therefore bioequivalent, so new clinical studies for generic drugs are not needed

15. What parameters are required to pass bioequivalence limits of 80% to 125% in Canada for an uncomplicated, standard oral drug product?

a) 90% confidence intervals of C_{max} and AUC
b) 90% confidence interval of AUC, and relative mean of C_{max}
c) Relative mean of AUC and 90% confidence interval of C_{max}
d) Relative mean of AUC and C_{max}

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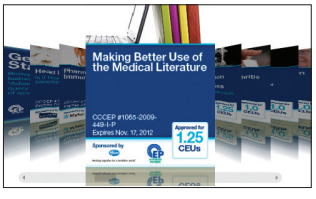

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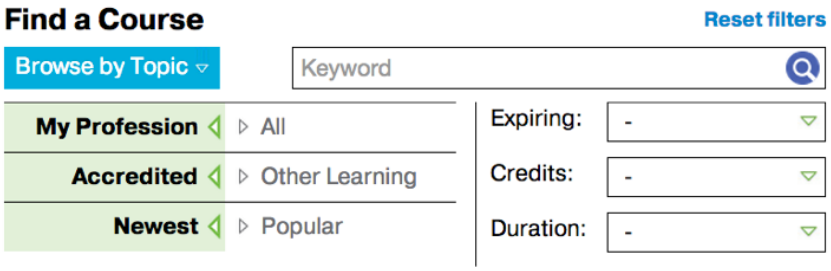

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