What Are Bioavailability and Bioequivalence?

All generic drugs in Canada are approved by Health Canada and have been shown to be bioequivalent to the Canadian Reference Product.[1,2] Any small differences in bioavailability between generic and brand name drugs permitted by the bioequivalence standards are not likely to be clinically significant.
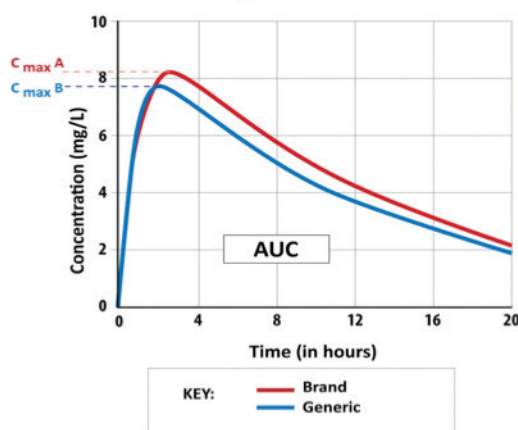
Bioavailability

Bioavailability is a measurement of the rate and extent to which a therapeutically active chemical is absorbed from a drug product into the systemic circulation and becomes available at the site of action.

For most drugs that are taken orally, the active ingredients are released in the gastrointestinal (GI) tract and arrive at their site of action via the systemic circulation. Blood concentrations of the active ingredients and/or their active metabolites thereby provide a marker for the concentration at the site of action and a valid measure of bioavailability.

A blood concentration-time curve (achieved by serial measurements over time) reflects not just the release of the active ingredient from the drug and its absorption from the GI tract, but also other factors including presystemic metabolism, distribution, and elimination.

Figure 1: Simulation of a Drug Concentration Versus Time Curve for Two Drug Products

KEY: Brand / Generic

C_{max} maximum plasma drug concentration;
AUC total area under the plasma drug concentration-time curve

Bioavailability is assessed using two main pharmacokinetic variables (see Figure 1):

- the area under the blood concentration versus time curve (AUC)
- the maximum blood concentration (C_{max}).

Bioequivalence

If two drugs are bioequivalent, there is no clinically significant difference in their bioavailability.

> "The bioequivalence standards we use in Canada have been in place for 20 years and are among the most rigorous in the world."
>
> — Eugenia Palylyk-Colwell, BScPharm, PhD; Member, Scientific Advisory Committee on Bioavailability and Bioequivalence, Health Canada

Although bioequivalence is most commonly discussed in relation to generic drugs, it is important to note that bioequivalence studies are also performed for brand name drugs in some situations such as:

- between early and late clinical trial formulations or between the formulations used in clinical trials and the product to be marketed for new drugs
- when changes in formulation have occurred after a brand name drug has been approved; for example, a change in one or more excipients (inactive ingredients).

Bioequivalence studies are a surrogate marker for clinical effectiveness and safety data, as it would not normally be necessary to repeat clinical studies for generic products. For oral drugs, it is accepted that if blood concentrations of the active ingredient of the generic and brand name drugs are the same, then their concentration at the site of action and therefore their safety and effectiveness will also be the same. For other dosage forms (e.g., drugs for inhalation, topical, or parenteral use), bioequivalence can be demonstrated through other comparative testing (e.g., comparative pharmacodynamic studies, pharmaceutical properties) in addition to or in lieu of comparative bioavailability to support the safety and efficacy of the proposed product.

Acceptance Criteria for Bioequivalence

The standards for bioequivalence in Canada are built upon internationally recognized standards and criteria and are amongst the highest in the world. Health Canada scientists ensure that the standards are adhered to and kept up to date as they work closely with an expert panel of scientists, physicians, and pharmacists from across Canada.

For oral drugs, bioequivalence is determined by comparing the relative bioavailability of the brand name drug versus the generic drug.

There must be no more than a 20% difference between the AUC and C_{max} of brand name versus generic products. This is based on international consensus that differences below this percentage rate are not clinically significant. In order to establish bioequivalence, the AUC and C_{max} for the generic drug are compared with that of the brand name drug (see Figure 1).

Bioequivalence is based on a comparison of ratios where the ratio of generic to brand name for each pharmacokinetic variable does not differ by more than 8:10. This is how the range for the confidence intervals is defined:

- 8/10 = 0.8 (gives the lower limit of 80%)
- 10/8 = 1.25 (gives the upper limit of 125%).

The ratio of the C_{max} and the 90% confidence interval for the ratio of the AUC should be contained within the limits of 0.8 to 1.25 (see Figure 2). Thus, bioequivalence is based on ratios where the nominal equality is 1 (or 100%). It is not based on differences in absolute values.

In practice, for a generic product to demonstrate bioequivalence, the ratio of the mean values must be close to 100% in order for the upper and lower limits to be contained within the accepted range. If the observed ratio is closer to 80% or 125%, then the data would have to contain little or no variation from the mean for the 90% confidence intervals of the ratio to lie within the 80% to 125% range necessary to demonstrate bioequivalence.[3]

This applies to generic drugs and aforementioned situations cited for new formulations of brand drugs.

Testing Bioequivalence in a "Normal and Healthy" Population

When a brand name drug is developed, evidence is required of its pharmacokinetic properties, efficacy, and safety in healthy volunteers, as well as the target patient population. However, bioequivalence studies are normally only performed in healthy volunteers in order to reduce the variability not related to differences between products.

Figure 2: Testing for Bioquivalence

Criteria for Acceptance: 90% confidence interval of the ratios of AUC falls between 0.80 and 1.25 of the branded drug

This raises the question as to whether the generic drug would perform differently in the target patient population, taking into consideration factors such as comorbidities, concurrent prescriptions, and physiological factors including differences in first pass metabolism, gastric pH, and bacterial flora.[4]

Scientifically, there is no reason to suppose that differences in metabolism that may affect the plasma disposition of an active ingredient from a brand name drug will not equally affect the plasma disposition of the same active ingredient from a generic drug.

Bioequivalence studies are usually crossover studies in which each subject acts as their own control. This model (in vivo healthy volunteers) is regarded as adequate for detecting formulation differences. The results obtained allow extrapolation to populations in which the reference product is approved (e.g., the elderly, children, patients with renal or liver impairment).

The Potential Effect of Excipients on Bioequivalence Studies

Bioequivalence studies usually involve single doses of a drug. It is theoretically possible that excipients used in the generic formulation (preservatives, pH adjusters, thickening agents, etc.) could affect the absorption and metabolism at steady state without producing these same differences in a single dose.[5] However, this is extremely unlikely and would normally be apparent from differences observed in the bioequivalence study.

Any difference that may exist is negligible compared with the variability of the conditions in the GI tract of patients and its effect on absorption.

Critical Dose Drugs[6]

In Canada, a few drugs have specifically been identified as "critical dose drugs." These drugs are highly toxic or are considered to have a narrow therapeutic range. Examples are cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, theophylline, and warfarin. Health Canada bioequivalence standards differ for these drugs:
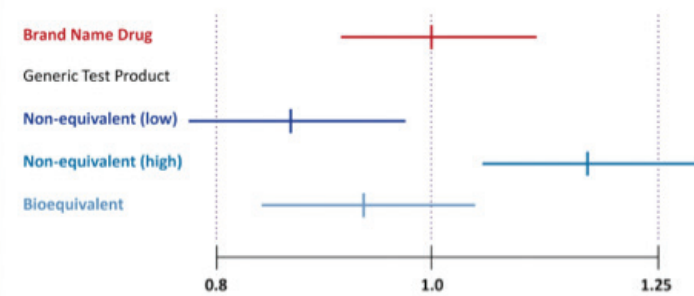
- The 90% confidence interval for the AUC ratio should be contained within tighter confidence limits (90% to 112%).

- The 90% confidence interval for the C_{max} should be contained within the limits of 80% to 125%.

- It is sometimes necessary to conduct steady-state studies (as opposed to single-dose studies for other drugs). In these cases, the 90% confidence interval for the C_{min} ratio should be contained within the limits of 80% to 125%.

- It is sometimes necessary to conduct studies in patients rather than healthy volunteers. In these cases, the study population should be as homogenous as possible.

- Studies must be conducted in both fasted and fed states (as opposed to a fasted state only for other drugs).

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