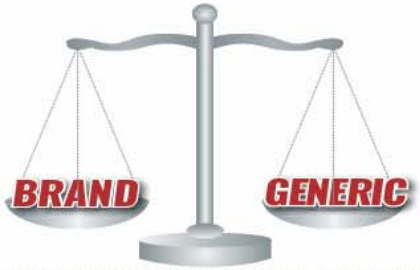
Bioequivalency of Medications

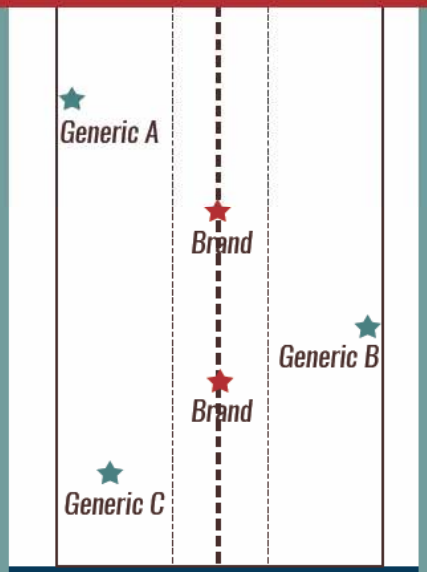
Making Much Ado Over What Is Most Often Little Ado



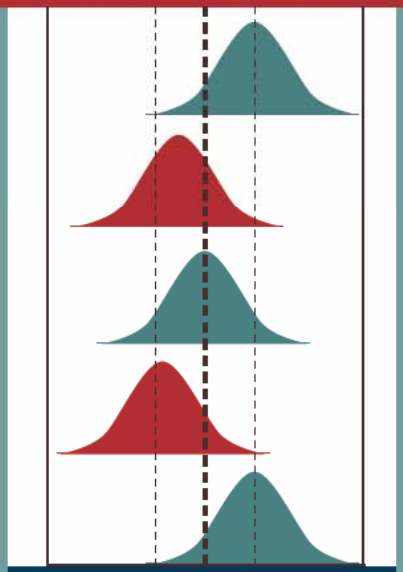
Rarely, there may be legitimate issues related to generics. From a regulation point of view, examples include problems found with Concerta and Wellbutrin (note: not Canadian formulations). There was a failure to identify product deficiencies early on, coupled with a slow response by the FDA to remove the products, both of which were concerning. Here are some considerations as to why these cases were very unexpected and are likely to remain isolated incidents.

# of published studies to date demonstrating meaningful clinical superiority of brand name medications over generic = 0

UNDERSTANDING HEALTH CANADA'S STANDARDS



COMMON MISCONCEPTION



REALITY

Bioavailability is assessed using two pharmacokinetic variables. Area Under the Curve (AUC) & Maximum Blood Concentration (Cmax). Drugs are bioequivalent if no significant difference in AUC or Cmax. For AUC, this means entire 90% CI must be within 80-125%.

- The brand has precisely 100% of stated content	- Brand and generic are subject to the exact same standards
- The "80-125 Rule" for AUCs applies to a single point	- The "80-125 Rule" applies to 90% confidence intervals
- There is an allowed, potential 45% variance	- There is an actual observed 5 to 7% variance

A STEPWISE APPROACH

There has been a clinical deterioration (e.g. drug less effective, or more pronounced side effects) AND a switch from brand to generic...

STEP 4
Consider changing manufacturers due to possible effects of different fillers, coatings, etc... i.e. try a different generic or brand.

STEP 3
Consider other temporal changes that could account for clinical change & are more likely e.g. patient frailty, change in weight, renal fluctuations.

STEP 2
Ensure patient is taking medication as prescribed & rule-out interactions (drug-drug/food/disease).

STEP 1
Ensure patient is aware the brand & generic are the same drug with perhaps different size, shape, colour, etc...

Steps to Consider (may take time)

References: *See RxFiles Detail Document: http://www.rxfiles.ca/rxfiles/uploads/documents/Bioequivalency-QandA-Links.pdf. Regier, L. April 2015.*

BIOEQUIVALENCY OF MEDICATIONS

Making *Much Ado* Over What is Most Often *Little Ado*

A balanced and accurate understanding of bioequivalency for brand name versus generic medications is sometimes sacrificed at the foot of those with vested interest. Recently, a case study raised this issue as the primary learning point, illustrating the exception rather than the norm and misrepresenting statistics.

Several publications have discussed common misunderstandings and misperceptions around bioequivalency. The links below will be helpful for those who want to better understand this area.

A few key points:

1) There can be and are differences in the bioavailability between various products.
2) It is possible but uncommon that differences in bioavailability are clinically significant
3) There are cases where differences may be clinically significant, and it is reasonable to entertain this possibility when assessing unexplained changes in medication effectiveness or tolerability.
4) The bioequivalence statistics, AUC and C_{max}, are often misrepresented, especially as it relates to the 90% confidence interval. Links on this page will be useful in better understanding and correctly contextualizing this concept for day to day practice. Of note…
   a. Allowed limits (i.e. 80 – 125%) translate into only ~3-4% difference on average between brand & generic
   b. Different batches of brand name drugs are allowed the same variance
   c. There is a narrower limit for "critical dose drugs" (e.g. warfarin) where the 90% CI for AUC is 90-112%
5) Remember, even if we could take the same person and give the same drug on different occasions, there would be some variation in the blood levels drawn due to fluctuations in physiological and testing factors. Bioequivalence standards allow for such variation as well as consideration for the clinical significance of any real variation.

For some good discussion on the area of bioequivalence check out the following links:

CADTH. What are Bioavailability and Bioequivalence? 2012
https://www.cadth.ca/media/pdf/Generic_prof_supplement_en.pdf
(Other CADTH links: a) www.cadth.ca/generics; b) http://hospitalnews.com/understanding-generic-drugs/)

Damm T. Generic vs Brand Name Drugs: What are the differences. In medSask newsletter. Dec 2013.
http://medsask.usask.ca/documents/hot-topics/Generic_vs_brand.pdf

McCormack J, Chmelicek JT. Generic versus brand name: the other drug war. Can Fam Physician. 2014 Oct;60(10):911. http://www.cfp.ca/content/60/10/911.full

AUC= area under the curve **CI**= confidence interval **Cmax**=concentration maximum