

# Bioequivalence of Generic Drugs: A Simple Explanation for a US Food and Drug Administration Requirement

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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## ABSTRACT

There is a widespread misconception that for a generic drug to be deemed bioequivalent to a branded drug, it must contain 80%–125% of the active ingredient that is present in the branded version. More correctly, bioequivalence is studied in randomized crossover trials that compare the generic drug with the reference agent, and the relevant outcome measures are pharmacokinetic (PK) parameters such as peak drug concentration and area under the curve, which describe the rate and extent of absorption of the drug. The ratio of each PK characteristic of the generic drug to the reference drug is computed; the ideal value of this ratio is 1:1, or just 1.00 (indicating a perfect match, or perfect bioequivalence). Because this ideal is probably unattainable, the US Food and Drug Administration requires that the 90% confidence interval of the PK ratio should lie between 0.80 and 1.25. For the entire 90% confidence interval to meet this requirement, the mean PK value of the generic product should actually lie quite close to that of the reference standard. Therefore, the variation between the generic and the reference is actually small. These concepts are explained in this article with the help of simple, easy-to-understand examples.

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## Clinical Issue

Many believe that the US Food and Drug Administration (FDA) requirement for bioequivalence (BE) of generic drugs allows a generic pill to contain as little as 80% or as much as 125% of its stated content. Actually, quite a lot is incorrect in such a belief. This article explains why the belief is wrong, what the right explanation is, and why it is important to know the difference.

## Introduction

A new drug has to meet stringent requirements related to safety and efficacy before it can be marketed; much is also required to be known about the pharmacokinetics (PK) and pharmacodynamics of the drug. Accordingly, a new drug has to be studied in animals, and then in phase 1 to phase 3 clinical trials in humans. When patent or exclusivity protection expires, laws allow generic versions of the drug to be marketed; the sole requirement is that the generic version must be pharmacokinetically bioequivalent to the patented, branded drug. The assumption is that if this is established, then the preclinical and clinical research findings related to the branded drug will also apply to the generic drug.

So, how is BE established? It is important that readers understand that mere milligram equivalence of the active ingredient in the generic formulation is not a sufficient criterion because differences in the rest of the contents (the excipients) might alter PK parameters such as how much of the drug is absorbed, how fast the drug is absorbed, what the peak blood levels are, and so on, all of which influence the safety and efficacy of the pill. Therefore, BE must be based on characteristics of the generic drug after it enters the body, that is, on the PK parameters of the drug.

The current position of the FDA is that BE is declared when there is no significant difference between the generic drug and the reference drug in the rate and extent to which the active ingredient becomes available when administered at the same dose under similar conditions and in an appropriately designed study.<sup>1</sup> The absence of significant difference is operationalized as follows: the entire 90% confidence interval (CI) of key PK parameters, such as peak concentration ( $C_{max}$ ) and area under the curve (AUC), must lie within 80% and 125% of the value for perfect BE.<sup>2,3</sup> There is, of course, much more to the FDA requirements, such as the manner in which the study needs to be designed and conducted and the data that need to be acquired in different situations and at different time points for different kinds of product; because there are far too many situations and requirements, the reader is referred to the FDA website at which the various documents can be accessed.<sup>4</sup> This article will focus on what is commonly misunderstood, which is the requirement that the 90% CI of a PK value must lie within 80% and 125% of the ideal.

## The Confidence Interval and the Reference Range: Starting With a Simplification

The concept is not easy to understand, and so here is a simplification of the idea; the full explanation is provided in the next section. Essentially,

- There are stringent requirements for a generic drug to be deemed bioequivalent to a branded reference. One requirement is that the rate and extent of absorption of the generic product should be closely similar to that of the reference.
- The peak drug concentration and the area under the curve are pharmacokinetic (PK) parameters that are commonly examined when studying bioequivalence in randomized crossover trials.
- For bioequivalence to be declared, the mean PK characteristics of the generic drug should closely match that of the reference. This is operationalized as follows.
  - The ratio of the mean PK value of generic to reference is computed; the ideal value of this ratio is 1.00, indicating perfect bioequivalence.
  - The entire 90% confidence interval of this ratio should lie between 0.80 and 1.25, indicating a high level of confidence that the population PK value of the generic is close to that of the reference.

a randomized crossover trial is conducted with the generic drug as the experimental agent and the branded drug as the control; PK outcomes such as (but not limited to)  $C_{max}$  and AUC are the outcomes of interest because these indicate the rate and extent of availability of the generic drug to be compared to the standard.

In such a study, it is not merely the observed PK value (eg,  $C_{max}$ , AUC) that is required by the FDA to lie within 80% and 125% of the reference value but the entire 90% CI of the observed PK value. To understand this, let us assume for the sake of convenience that the mean AUC of the reference product is 100 units in the crossover study that has been conducted. The FDA requirement (simplified, in this section) is that the mean AUC of the generic product (as observed in the crossover study) as well as its entire 90% CI must lie between 80 and 125 units.

Because there is no assurance that the AUC estimate for the generic drug in this study is representative of all the batches of the generic drug in all patients in all studies, to obtain an idea of where the population mean for the AUC lies, we need to compute the CI around the observed mean. Let us assume that the observed mean AUC for the generic drug in this study is 95 and that the 90% CI is calculated to be 82 to 108. Because the mean AUC and its 90% CI lie entirely within the 80–125 unit range, these hypothetical results meet the FDA requirement for pharmacokinetic bioequivalence (at least with regard to AUC).

In another hypothetical study, the observed mean AUC value for the generic drug was 86 and the 90% CI was 75 to 97. In this example, part of the CI falls below the lower limit of 80 that is set by the FDA. This means that there is a possibility that the population mean for the AUC of the generic drug is less than the lowest permissible value. Therefore, the results do not meet the FDA criteria for bioequivalence.

From these examples, it should be fairly obvious that if the entire 90% CI has to fall within the 80–125 unit range, then the mean PK value obtained with the generic drug should be close to the mean PK value of the standard. In other words, it is a misconception that the FDA allows the strength of a pill, or a PK parameter, for that matter, to vary from 80% to 125% of the standard.

Of course, we cannot be assured that the mean PK value of all the batches of that generic drug in all patients and in all studies (that is, the population mean) will be identical with the mean value obtained in the described study (the sample mean). We are merely 90% confident that the population mean will lie within the CI range specified and that this range lies within 80%–125% of the ideal, that is, close to the ideal. A more detailed discussion on the interpretation of CIs is provided elsewhere.<sup>5</sup>

### The Confidence Interval and the Reference Range: A More Accurate Explanation

The most obvious shortcoming of the explanation provided in the preceding section is that it assumes that the mean PK value of the reference drug (as observed in the crossover study) is a perfect standard. However, this is not so; it is also an estimate. For example, if we find that the AUC of the reference drug is 100 units in the BE study, we cannot assume that it will be 100 at all times, that is, across all batches of the reference drug in all patients and in all studies.

Because there can be variation in the observed PK value of the reference drug as well as that of the generic drug, the FDA requires that the BE statistics be based not on the observed PK values but on the ratio of the PK values of the generic and reference drugs. If the PK values are identical, as when BE is perfect, then the ratio will be 1:1; that is, 1.00. In such an event, the 80%–125% range becomes 80%–125% of 1.00, which is 0.80–1.25.

Here is an example of the results of a hypothetical study. The mean AUC of the reference drug is 25 units. The mean AUC of the generic drug is 29 units. The ideal ratio of generic to reference AUC is 1:1, that is, 1.00, implying that the AUCs of the 2 drugs are identical. In the study conducted, the ratio of the mean AUCs of the generic to reference drugs is 29/25, or 1.16. This means that the bioavailability of the generic drug exceeds that of the reference drug by a mean of 16%. The 95% CI of the ratio is calculated and found to be 1.03 to 1.30. Because the upper bound of this CI (1.30) exceeds the permissible upper limit (125% of 1.00, that is, 1.25), the generic drug cannot be said to be bioequivalent to the reference drug.

Consider another example. The mean AUC of the reference drug is 42 units, and that of the generic drug is 38 units. The observed AUC ratio is 38/42, or 0.90. This means that the generic drug has, on average, 10% lower bioavailability than the reference drug. However, the 90% CI is found to be 0.82 to 0.98. Because the entire 90% CI lies within 80% and 125% of the ideal (that is, between 0.80 and 1.25), it is concluded that the 2 drugs are bioequivalent.

As in the preceding section, readers may note that the mean PK value of the generic drug must be quite close to that of the reference drug for the ratio of the PK values to be close to 1.00 (implying comparable bioavailability); if the ratio is not close to 1.00, then the 90% CI of the ratio is unlikely to lie between 0.80 and 1.25.<sup>3</sup>

### Statistical Notes

1. For reasons related to the nature of the data and the statistical assumptions for testing, the exercises described above are conducted on geometric means and not on arithmetic means; and the data require to be logarithmically transformed as a prelude to analysis. The FDA has provided detailed guidance on statistical methods for BE studies.<sup>2</sup>

2. The reason why 90% CIs are computed instead of the more customary 95% CI is that in BE studies, 1-sided hypotheses are examined at the 5% level at both upper and lower levels, which translates to a 90% CI.<sup>2</sup>

3. According to the FDA, the BE limit of 80%–125% is based on a clinical judgment that a test product with bioavailability that falls outside this range should be denied market access.<sup>2</sup>

4. If this 80%–125% range seems to allow for a wide margin of error, readers may note that PK values commonly vary 10-fold (1,000%) or more across individuals, and so the 80% to 125% (45%) range around the ideal is actually quite a small variation. However, it must be noted that the 10-fold variation is between individuals whereas the 45% variation permissible in BE studies is within individuals.

### Practical Notes

This article explains that the FDA requirement for BE between generic and patented drugs is actually quite stringent, and not lax, as many mistakenly believe. Clinicians who do not realize this may favor branded drugs over generics, thereby substantially increasing the cost of treatment, or they may be skeptical of the efficacy of generics, thereby diminishing the placebo element in the psychopharmacologic response to generics if the skepticism is consciously or unconsciously communicated to the patient.

### Parting Notes

Other articles discuss the merits and demerits of generic and branded drugs<sup>6–9</sup>; here, the reader's attention is drawn to 2 points that are not commonly considered:

1. Sometimes, clinical differences between generic and branded drugs may be due to differences in their excipients; these do not need to be identical between generic and branded versions. An example is when allergic events (to excipients) differ between generic and branded drugs.<sup>10</sup>
2. Studies that show changes in efficacy or adverse effect outcomes when switching between generic and branded drugs are usually based on situations in which a generic drug is substituted for a branded drug in patients who are stable on the branded drug. These studies are therefore biased toward identifying poorer outcomes with the generic drug. Perhaps if patients who are stable on a generic drug are recruited, they may show poorer outcomes if they are instead prescribed a branded equivalent.<sup>11</sup> Problems in the conduct and interpretation of such studies include issues related to blinding and preconceived ideas; these will influence the placebo and nocebo outcomes.

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