Drug Interchangeability (Prescribability and Switchability) – Do We Have a Right Tool for the Assessment?

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Abstract

Bioavailability and bioequivalence studies play a vital role in the development of generic medicines. These studies help us in understanding the drug efficacy and safety and to compare against the reference listed drug (RLD). In the recent years, many debates have emerged about usage of average bioequivalence and whether it's a right tool for the assessment of narrow therapeutic index drugs and highly variable drugs. In this scenario, alternative approaches like population bioequivalence and individual bioequivalence have emerged. This paper aims to discuss all the important questions concerning whether these approaches, average bioequivalence, population bioequivalence and individual bioequivalence address the drug interchangeability and what is the level of accuracy for the assessment of different categories of drugs such as large therapeutic index drugs, narrow therapeutic index drugs and highly variable drugs.

Concerning precision, the three criteria could be considered in the following order:

> **Individual Bioequivalence > Population Bioequivalence > Average Bioequivalence**

Keywords: Drug Interchangeability, Prescribability, Switchability, Average Bioequivalence, Individual Bioequivalence, Population Bioequivalence.

INTRODUCTION AND BACKGROUND

Generic drugs are important options that allow greater access to health care for all. A generic drug is identical -- or bioequivalent -- to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies in US. Even more billions are saved when hospitals use generics.[1]

An estimated half of all prescriptions in the United States are filled with generic drugs. These products carry all the medicinal qualities (and side effects) of their brand-name counterparts, but generics tend to have one additional benefit: lower cost.[2]

Debate around generic drugs efficacy and safety is not a recent issue. The introduction of generic medicines in the US market came in 1984, through the Drug Price Competition and Patent Restoration Act (also known as Hatch-Waxman Act). By then, several discussions on drug efficacy and safety had been raised, with the concepts of bioavailability and bioequivalence as centre topics.[3]

Since the American Food and Drug Administration (FDA) introduced regulations for bioequivalence and bioavailability studies in 1977, methodology and criteria for proof of bioequivalence have been the object of many debates and improvements, [4] having served as regulatory milestones for different countries. In Brazil, for instance, the Generic Drug Law[5] was introduced on February 10th 1999, with the technical regulation originally issued by the local regulatory agency, ANVISA (*Agência Nacional de Vigilância Sanitária*), on August 9th 1999.[6] In 1992, the FDA published its first guide on statistical procedures for *in vivo* bioequivalence studies and established average bioequivalence as the criterion for bioequivalence assessment between the test drug and the reference drug.[7] Similarly, the same criterion was adopted by ANVISA in 2003.[8]

In spite of great improvements over the last years, many debates have been raised around the usage of average bioequivalence as the sole criterion for all drug categories, mainly for those, which have a narrow therapeutic range, and also for those, which display great intra- or inter-subject variability. For such categories, population and individual bioequivalence have appeared as alternative criteria for bioequivalence assessment.[7,9-11] In 1999, FDA issued a draft guidance concerning several criteria for bioequivalence proof – the Average, Population and Individual approaches to establishing bioequivalence.[12] In 2001, it also published a guide covering statistical aspects of average, population and individual bioequivalence – the FDA guidance on statistical approaches to establishing bioequivalence.[13]

THE IMPORTANCE OF THE PROPOSED ASSESSMENT
Issues on efficacy and safety for generic drugs

The substitution of a branded reference drug for a generic counterpart has been surrounded by the discussion on efficacy and safety issues by patients, physicians, pharmacists and other health professionals.[14]

The first issue refers to a more general aspect on safety and efficacy:

(i) Are generic drugs as effective and safe as the reference drugs?. Considering the two basic situations under which generic drugs could be prescribed, [9] two other issues have been raised.

In the first situation, considering a recently diagnosed patient,

(ii) is beginning treatment with a generic drug as safe and effective as with a reference drug? For the second situation, considering a patient who is already in treatment with a reference drug and wishes to change it for a less expensive alternative,

(iii) is it safe and effective to make a substitution from a reference drug to its generic counterpart?

Bioequivalence evaluation should provide answers to such questions – the challenge being the definition of the main parameters for BE evaluation, which would allow each question to be tackled appropriately.

When a generic drug is considered bioequivalent to a reference drug, they are assumed to be therapeutic equivalents and therefore to have the same efficacy and safety profile.[4] It is also assumed that original efficacy and safety have been evaluated and established during the approval process for the reference drug. In such a situation, the average of bioavailability for the test drug (to become a generic) and the reference drug (μT; μR) is enough to ensure efficacy and safety. Therefore, with this parameter, it is concluded that the generic drug is as effective and safe as its reference counterpart for a given population, thus answering the first question posed.[15,16]

The second question refers to the situation in which a generic drug is to be prescribed for the initial therapeutic treatment of a patient. It comprises the definition of interchangeability for a new patient – also known as **prescribability**. For such a situation, one should also take into account inter-subject variability. Consequently, it should be important to compare observed bioavailability distribution and not only average bioavailability. In other words, besides average bioavailability, variances between the test drug and the reference drug (S_{TT}^2 e S_{TR}^2) should also be considered as relevant parameters.[9]

The third question is related to interchangeability for a patient already in treatment – also known as **switchability**. In this scenario, a bioequivalence criterion should contemplate parameters covering intra-subject variability and also the variability resulting from interaction between subject and formulation. So, bioavailability variances for each drug within the same subject should be contemplated (S_{WT}^2, S_{WR}^2), as well as the subject-by-formulation variance (S_D^2).[9]

Average bioequivalence and interchangeability

The average bioequivalence criterion stipulates that two drugs are to be considered bioequivalent when the 90% confidence interval, considering the average bioavailability of the test drug (T) and the reference drug (R) and the T/R ratio, is between 80.00% and 125.00%, for data converted to the logarithmic scale. The result is expressed as average bioequivalence (ABE), as it compares average values for both test and reference drug bioavailabilities.[11,15] ABE

determination is based solely on the comparison of population averages for selected pharmacokinetic measurements – and not on the variances for such measurements (intersubject variance). Variance associated with interaction between individuals and formulations and intra-subject variance are not considered either.[11,15,19] Consequently, ABE criterion cannot fully answer all questions related to interchangeability – whether related to a new patient (prescribability) or to a patient in treatment (switchability) – for low therapeutic range drugs.[15,16,17]

Regulatory acts based on average bioequivalence establish that generic drugs can be used as substitutes for the corresponding reference drugs when bioequivalence is proved between both.

It is not stated that two different generics for a reference drug could be interchangeable, considering that both have established bioequivalence with the same reference. Nevertheless, bioequivalence between generics is not required.[17]

Some other issues have been raised around the ABE criterion, such as: (i) is the adoption of a single acceptance limit range valid for all pharmaceutical substances? and (ii) are bioequivalence requirements enough for substances with a high variability in pharmacokinetic parameters?[14,16]

The adoption of a single acceptance limit range for all drug substances has been under scrutiny, especially for those which display a narrow therapeutic range, where slight changes in concentration may lead to great changes in pharmacodynamics, such as digoxin, carbamazepine, levothyroxine and warfarin etc.,[17,19] For such drugs, interchangeability may be affected and more rigid limits have been recommended. On the other hand, for large therapeutic range drugs, such as oral antibiotics, antacids, antihistaminic agents and some analgesics, more flexible limits have been suggested.[13] Literature shows that assessing bioequivalence for drugs with a high pharmacokinetic variability, such as verapamil and nadolol, may be a very complex matter.[4] High variability drugs are defined as those for which intra-subject variability in pharmacokinetic parameters (maximum plasmatic concentration – C_{max} and/or area under curve – AUC) is equal to 30% or higher.[18] Bioequivalence determination for such drugs is complex as it requires a great number of subjects in order to give statistical power to the analysis.[4] For most other drugs, bioequivalence through ABE method can be determined with a small number of subjects, ranging from 18 to 24.[15]

Considering the natural limitations of the average bioequivalence, two other criteria for BE determinations have been suggested: population bioequivalence and individual bioequivalence.[13,17]

Population bioequivalence and individual bioequivalence

The main reason for the suggestion of these two new criteria is the need for more adequate answers to important issues referring to bioequivalence that may come up during the approval process for a new medicine or after-market launch.[7]

During the approval process, one important issue that might be raised is whether patients who have initiated treatment

with a generic drug will have the same results in terms of efficacy and safety as patients under treatment with the reference drug. Such an issue is related to interchangeability for a new patient or prescribability.[7,12,13] Population bioequivalence (PBE) takes into account inter-subject variability (inter-subject variance) and, therefore, tackles the issue of interchangeability for a patient who needs to start treatment.[9,14] Similarly, after market launch, safety and efficacy might be discussed when a medicine substitution is made. Such a situation is related to interchangeability for a patient in treatment or switchability.[7,12,13] Individual bioequivalence (IBE) takes into account intra-subject and subject-by-formulation variances, being a relevant criterion to tackle changes in treatment, when a reference drug is substituted for its generic counterpart, for instance.

IBE also allows a more precise evaluation of bioequivalence for drugs with high pharmacokinetic variability and also for those with narrow or large therapeutic range.[9,13] A retrospective analysis, based on 28 data sets originated from 20 replicate design crossover studies, shows lack of consistency in bioequivalence results evaluated for the three different criteria. Among the 28 data sets related to AUC (area under curve), 23 have been approved by ABE criterion, 27 by PBE and 22 by IBE. Among the five data sets not approved by ABE criterion, four were equally not approved by IBE – on the other hand, all five of them were approved by PBE criterion. Differences were even greater for the maximum plasmatic concentration (C_{max}) parameter.[7]

A bioequivalence study for two brands of amoxicillin/clavulanic acid 250/125 mg, conducted to compare ABE and IBE results, indicated an average bioequivalence between formulations, but not an individual bioequivalence.[19] Authors concluded that individual bioequivalence could be a more appropriate statistical tool to assess intra-subject variances and also subject-by-formulation interaction variances compared with average bioequivalence.

Concerning precision, the three criteria could be considered in the following order: **individual > population > average.**[14] Regarding study types, both ABE and PBE can be evaluated with two-period, non-replicate cross studies. IBE requires three period or four-period replicate studies.[20] Table I resumes main characteristics for each of the three bioequivalence criteria.

TABLE I: Bioequivalence Types and Evaluation Criteria	
Bioequivalence/ Parameters	**Evaluation Criteria**
Average Bioequivalence (ABE) Population Averages (μ_T; μ_R)	$(\mu_T; \mu_R) \leq BE$
Population Bioequivalence (PBE) Population Averages (μ_T; μ_R) Total Variances (S_{TT}^2 ø S_{TR}^2)	$\dfrac{(\mu_T; \mu_R)^2 + (S_{TT}^2 - S_{TR}^2)}{S_{TR}^2}$
Individual Bioequivalence (IBE) Population Averages (μ_T; μ_R) Intra-Subject Variances (S_{WT}^2, S_{WR}^2) Subject-by-formulation interaction variances (S_D^2)	$\dfrac{(\mu_T; \mu_R)^2 + (S_{WT}^2 - S_{WR}^2) + S_D^2}{S_{WR}^2}$

OVERVIEW OF THE RELEVANT LITERATURES

Lopes N et al., (2009) studies the utilization of average bioequivalence as the only criterion of evaluating bioequivalence for all drug categories and population, individual bioequivalence were presented as alternative criteria. He further discussed, especially about the interchangeability aspect, and emphasises the main differences among these three methodologies: average, population and individual bioequivalence. ABE limitations for highly variable drugs and narrow therapeutic drugs are known and may be addressed by modification of the acceptance limits[20]. However, studies with replicate design have been considered to evaluate highly variable drugs/drug products,[20] which is an indication that the use of population and individual bioequivalence may be an alternative to ABE for specific drug products. He further added that at the present time, these approaches are recommended by the FDA only under special circumstances, when there is need for more precise bioavailability measurements than those resulting from the average bioequivalence criterion.[21]

Kiyohito Nakai et al., (2000) studied and discussed that average bioequivalence is insufficient for assessing switchability between two formulations. The average bioequivalence approach compares only the mean parameters of the test and reference formulations in the subject groups. But population bioequivalence approach guarantees prescribability by assessing the total variances of bioavailability values of the test and reference formulations in addition to the

average bioequivalence. The individual bioequivalence approach guarantees switchability from the reference formulation to the test formulation by assessing the intrasubject and subject-by-formulation interaction in addition to the average bioequivalence. He further stated that the individual and population bioequivalence approaches are the more appropriate study methods to assure the high quality of generic products as compared with the average bioequivalence approach.[22]

Laszlo Endrenyi et al., (1997) discussed that Individual bioequivalence takes into account not only the difference between the average kinetic responses but also the subject-formulation interaction and the contrast of intrasubject variations of the two drug products. The new approach is concerned with the switchability of formulations within individuals instead of the prescribability, on the average, of a new test product. Thus, individual bioequivalence is a certainly interesting and potentially very valuable method assessing substitutions of drug formulations. He further stated that various regulatory and technical issues still require resolution and suggested that more research and experience is necessary before the questions can be answered satisfactorily and appropriately.[23]

Laszlo Endrenyi et al., (1998) stated that the rationale and principles of the procedure proposed for the adoption of individual bioequivalence is attractive and merit further scientific discussion. He further stated that the proposed procedure should not be implemented in its present form without further research and analysis to establish its validity and utility.[24]

REGULATORY AGENCIES STAND IN HANDLING DIFFERENT CATEGORIES OF DRUGS

Different regulatory agencies recommend different approaches to ensure that the efficacy and safety of large therapeutic range drugs, narrow therapeutic range drugs and highly variable drugs. The same is discussed here.

United States of Food and Drug Administration (USFDA)

Large Therapeutic Drugs

USFDA recommends that the traditional BE limit of 80.00% to 125.00% for non-narrow therapeutic range drugs.[25]

Narrow Therapeutic Range Drugs

As per the guidance "Bioavailability and Bioequivalence studies for orally administered drug products – General Considerations, March 2003", unless otherwise indicated by a specific guidance, this guidance recommends that the traditional BE limit of 80 to 125 percent for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and C_{max}) of narrow therapeutic range drugs.[25]

As per the recent update and recommendation from FDA, Irrespective of the molecule, Single-dose, 4-way, fully replicated crossover design in-vivo study in fasting and fed condition needs to be planned. Fully replicated crossover design is recommended to scale bioequivalence limits to the variability of the reference product and to compare test and reference product within-subject variability.[26]

Use the unscaled average bioequivalence procedure to determine BE for individual PK parameter(s). Every study should pass the scaled average bioequivalence limits and also regular unscaled bioequivalence limits of 80.00-125.00%.[26]

Highly Variable Drugs

As per USFDA recommendation, "Partial or fully replicated crossover design in-vivo study needs to be planned". Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or C_{max} (i.e., within-subject variability $\geq$ 30%).

Determine S_{WR}, the within-subject standard deviation (SD) of the reference product, for the pharmacokinetic (PK) parameters AUC and C_{max}.

a). If SWR < 0.294, use the two one-sided tests procedure to determine bioequivalence (BE) for the individual PK parameter(s)

b). If SWR $\geq$ 0.294, use the reference-scaled procedure to determine BE for the individual PK parameter(s)

For the test product to be bioequivalent to the reference product, both of the following conditions must be satisfied for each PK parameter tested:

a). the 95% upper confidence bound for

$$\left(\bar{Y}_T - \bar{Y}_R \right)^2 - \theta s_{WR}^2 \text{ must be} \leq 0$$

AND

b). the point estimate of the Test/Reference geometric mean ratio must fall within [0.80, 1.25][27]

European Medicine Agency (EMEA – European union)

Large Therapeutic Range Drugs

In studies to determine bioequivalence after a single dose, the parameters to be analysed are $AUC_{(0-t)}$, or, when relevant, $AUC_{(0-72h)}$, and C_{max}. For these parameters, the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80.00- 125.00%.[28]

Narrow Therapeutic Index Drugs

In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where C_{max} is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter.[28]

Highly Variable Drugs

Highly variable drug products **(HVDP)** are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out.[28]

Those HVDP for which a wider difference in C_{max} is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for C_{max} can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for C_{max} of the reference compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.[28]

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to [U, L] = exp [±k·sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the within-subject standard deviation of the log-transformed values of C_{max} of the reference product. The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology.[28]

Within Subject CV (%)★	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
$\geq$ 50	69.84	143.19

★ CV (%) = $100 . \exp^{(MSE-1)0.5}$

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%. The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the

acceptance range should remain at 80.00 – 125.00% regardless of variability. It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.[28]

Therapeutic Goods Administration (TGA-Australia)[29]

Bioequivalence evaluation is similar to EMEA recommendations.

Therapeutic Products Directorate (TPD-Canada)

Large Therapeutic Range Drugs

Irrespective of the molecule category (Large Therapeutic Range Drugs, Narrow Therapeutic Index Drugs, Highly Variable Drugs), to determine bioequivalence, the following standards will be obtained in single dose cross-over comparative bioavailability studies.[30]

a) The 90% confidence interval of the relative mean area under the concentration versus time curve to the time of the last quantifiable concentration (AUC_T) of the test to reference product should be within 80.0% to 125.0% inclusive.[30]

b) b) The relative mean maximum concentration (C_{max}) of the test to reference product should be between 80.0% and 125.0% inclusive.[30]

Narrow Therapeutic Index Drugs/ Critical Dose Drugs

Critical dose drugs are defined as those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious.

For these drugs:

a) The 90% confidence interval of the relative mean AUC* of the test to reference formulation should be within 90.0% to 112.0% inclusive.

[* This refers to the relevant AUC for the type of study and drug involved, for example (e.g.), it could refer to AUC_T, or AUC_{tau} for multiple dose-studies, or AUC_{0-72h} for drugs with a half-life greater than 24 hours.]

b) The 90% confidence interval of the relative mean C_{max} of the test to reference formulation should be between 80.0% and 125.0% inclusive.

These requirements are to be met in both the fasted and fed states.[30]

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} of the test to reference formulation should also be between 80.0% and 125.0% inclusive.[30]

Highly Variable Drugs

For the purpose of bioequivalence testing, there is no compelling need for a distinct category of "highly variable" drugs, given that there is sufficient permitted flexibility in study design to address exceptional cases. For example, it may be possible to justify, *a priori*, conducting the study in a pre-screened sub-population such as slow metabolizers, in which the variability may be lower for the particular drug being studied. This type of flexibility in study design does not require the application of special bioequivalence standards.[30]

Medicine Control Council (MCC- South Africa)

Large Therapeutic Range Drugs

i) **AUC_t - ratio**

The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %).[31]

ii) **C_{max} - ratio**

The 90 % confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133 %, calculated using log-transformed data.[31]Narrow Therapeutic Index Drugs

i) **AUC_t - ratio**

The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %).[31]

ii) **C_{max} - ratio**

The 90 % confidence interval for the test/reference ratio should lie within an acceptance interval of 80 – 125 %, calculated using log-transformed data.

Use of alternative methods should be stated *a priori* in the protocol and cannot be added retrospectively.[31]

Highly Variable Drugs

i) **AUC_t - ratio**

The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %).[31]

In certain cases an alternative approach may be acceptable.[31]

Justification for the use of alternative methods, e.g. scaled average bioequivalence (ABE) based on sound scientific principles for the evaluation of the bioequivalence of highly variable drugs/APIs, has been described in the literature (References 2 and 3). Use of alternative methods should be stated *a priori* in the protocol and cannot be added retrospectively.[31]

ii) **C_{max} - ratio**

The 90 % confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133 %, calculated using log-transformed data.

In certain cases, e.g. in the case of highly variable API's, a wider interval or other appropriate measure may be acceptable, but should be stated *a priori* and justified in the protocol.[31]

DO WE HAVE A RIGHT TOOL FOR THE ASSESSMENT?

Health professionals and consumers can be assured that regulatory approved generic drugs have met the same rigid standards as the innovator drug. To gain regulatory approval, a generic drug must:

- contain the same active ingredients as the innovator drug (inactive ingredients may vary)
- be identical in strength, dosage form, and route of administration

- have the same use indications
- be bioequivalent
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products[1]

Although bioequivalence might not be a recently established parameter, there are still debates in search of more precise evaluation criteria. As such criteria are able to tackle efficacy and safety issues, frequently raised by clinical practice; they could be incorporated in further discussions by regulatory agencies. Meanwhile, in spite of publications commenting on the limitations of average bioequivalence, it remains the most frequently recommend criterion by regulatory agencies.[8,13,20] ABE limitations for highly variable drugs and narrow therapeutic drugs are known and may be addressed by modification of the acceptance limits[32]. However, studies with replicate design have been considered to evaluate highly variable drugs/drug products,[32] which is an indication that the use of population and individual bioequivalence may be an alternative to ABE for specific drug products. At the present time, they are recommended by the FDA only under special circumstances, when there is need for more precise bioavailability measurements than those resulting from the ABE criterion.[13]

The substitution of a branded reference drug for a generic counterpart has been surrounded by the discussion on efficacy and safety issues by patients, physicians, pharmacists and other health professionals.[14]

Considering the general aspect on safety and efficacy the below questions arise.
1. Are generic drugs as effective and safe as the reference drugs?
2. Is beginning treatment with a generic drug as safe and effective as with a reference drug? - **Prescribability**.
3. is it safe and effective to make a substitution from a reference drug to its generic counterpart? –
4. Switchability.

When a generic drug is considered bioequivalent to a reference drug, they are assumed to be therapeutic equivalents and therefore to have the same efficacy and safety profile.[4] It is also assumed that original efficacy and safety have been evaluated and established during the approval process for the reference drug. In such a situation, the average of bioavailability for the test drug (to become a generic) and the reference drug (μT; μR) is enough to ensure efficacy and safety. Therefore, with this parameter, it is concluded that the generic drug is as effective and safe as its reference counterpart for a given population, thus answering the first question posed.[15,16]

Average bioequivalence approach does not ensure the prescribability and switchability precisely. In this scenario, the alternative approaches like population and individual bioequivalence will be an ideal procedure to ensure the prescribability and switchability. Especially this will be a problem when we handle highly variable drug products and narrow therapeutic range drugs. As discussed in the previous sections, different regulatory agencies have

different study procedures including bioequivalence acceptance criteria.

There are very limited work was conducted in assessing prescribability and switchability related aspects of generic drugs. The future research will help us in understanding the study outcome based on average, population and individual bioequivalence approaches and based on the precision, which bioequivalence assessment approach will be appropriate for the evaluation of highly variable drugs, narrow therapeutic range drugs and large therapeutic range drugs.

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