Introduction
Debate around generic drugs efficacy and safety is not a recent issue. In the very beginning of the last century, the US Congress approved the Biologics Control Act – dating from July 1st 1902, it established the need for annual licensing of companies that manufactured and sold vaccines and serum derivatives. From that time on, labels for such products were required to contain the manufacturer’s name and licence number, and production was to be supervised by qualified professionals.1

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.1

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,2 having served as regulatory milestones for different countries. In Brazil, for instance, the Generic Drug Law3 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 1999.4 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.5 Similarly, the same criterion was adopted by ANVISA in 2003.6

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.5,7-9

This article discusses some of the issues concerning the use of average bioequivalence as criterion for bioequivalence (BE) evaluation and also highlights the main differences among the three bioequivalence methodologies – average (ABE), population (PBE) and individual (IBE).

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.12

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,7 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.

**Main parameters in bioequivalence for interchangeability**

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. 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.13,14

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 (sT2 and sR2) should also be considered as relevant parameters.7

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 (Ssw2 and Ssw2), as well as the subject-by-formulation variance (Ssb2).7

**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% and 125%, 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. ABE determination is based solely on the comparison of population averages for selected pharmacokinetic measurements – and not on the variances for such measurements (inter-subject variance). Variance associated with interaction between individuals and formulations and intra-subject variance are not considered either.11,13 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.1,12,15

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.15

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?12,14

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. 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. 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.15 Bioequivalence determination for such drugs is complex as it requires a great number of subjects in order to give statistical power to the analysis.2 For most other drugs, bioequivalence through ABE method can be determined with a small number of subjects, ranging from 18 to 24.13

Considering the natural limitations of the average bioequivalence, two other criteria for BE determination have been suggested: population bioequivalence and individual bioequivalence.11,15

**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.2

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.\textsuperscript{7,10,11} 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.\textsuperscript{7,12}

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.\textsuperscript{5,10,11} 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.\textsuperscript{7,12}

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 (Cmax) parameter.\textsuperscript{5}

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.\textsuperscript{17} 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.\textsuperscript{12} 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.\textsuperscript{12} Table 1 resumes main characteristics for each of the three bioequivalence criteria.

**Final considerations**

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.\textsuperscript{5,17,18} ABE limitations for highly variable drugs and narrow therapeutic drugs are known and may be addressed by modification of the acceptance limits\textsuperscript{20}. However, studies with replicate design have been considered to evaluate highly variable drugs/drug products,\textsuperscript{20} 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.\textsuperscript{11}

### Table I: Bioequivalence types and evaluation criteria

<table>
<thead>
<tr>
<th>Bioequivalence/Parameters</th>
<th>Evaluation criteria</th>
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<tbody>
<tr>
<td>ABE</td>
<td>Population averages ($\mu_T; \mu_R$) $\leq$ BE$^*$</td>
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<tr>
<td>PBE</td>
<td>Population averages ($\mu_T; \mu_R$), Total variances ($s_{TT}$) $\leq$ BE$^*$</td>
</tr>
<tr>
<td>IBE</td>
<td>Population averages ($\mu_T; \mu_R$), Intra-subject variances ($s_{IT}$), Subject-by-formulation interaction variance ($s_{p}$) $\leq$ BE$^*$</td>
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*BE limit; Modified from Chen; ABE = Average Bioequivalence; PBE = Population Bioequivalence; IBE = Individual bioequivalence*

\textsuperscript{References:}