

# Generic - equivalent drugs use in internal and general medicine patients: distrust, confusion, lack of certainties or knowledge?

## Part 1. Pharmacological issues

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### ABSTRACT

Despite compelling evidence and guidelines, in Italy, generic/equivalent drugs are still underused. The failure to adopt existing generic drugs may result into a missed opportunity to further reduce healthcare costs. Equivalent drugs are approved based on data deriving from bioequivalence studies. In the first part of the article, the concepts of generic/equivalent drugs are defined, emphasizing the differences between pharmaceutical equivalence, therapeutic equivalence, bioequivalence and bioavailability. A summary of the methods adopted to define bioequivalence (pharmacokinetic studies; pharmacodynamic studies; comparative clinical trials; *in vitro* studies) is also included.

### Introduction

A generic drug is a medicine that is developed to be the same as another drug which has already been authorized (the *reference medicine* or *originator*). In comparison with the reference product, a generic medication has the same active ingredient/s and is used at the same dose/s to treat the same diseases. Among the general public, a drug named *generic* is often perceived as a kind of *passepourtout* remedy, similar, but not equal to one or more medicines used to treat the same disease. For this reason, the *generic* products have been renamed *equivalent* (L. 149 26 July 2005).<sup>a</sup> Among cli-

nicians, it would be very helpful to share a common glossary of these different definitions (Table 1).

Healthcare authorities and policymakers tend to encourage the use of generics, mainly for economic reasons; however the replacement of brand-name products with the corresponding generic drugs is still highly controversial and affected by biases on the part of both healthcare providers and patients. As a result, in Italy, despite compelling evidence and guidelines, generic drugs are still underused, thus leading to a missed opportunity to further reduce healthcare costs.<sup>1</sup> In Italy, unlike other international markets, the *equivalent drugs* still have a limited market share, whereas, in Europe, they account for 40% in terms of average volume and 20% of the total spending. On the contrary, in Italy in 2010 their penetration did not exceed 6% of the total market with a lower share in the southern regions compared with the North.<sup>2</sup> On a sample of hospitalized elderly people, less than 50% of respondents think that generic drugs are as effective or as safe as brand-name medications.<sup>3</sup> According to a survey carried out in 2012

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Key words: generic drugs, equivalent drugs, drugs with expired patent, pharmacological issues, pharmaceutical equivalence, therapeutic equivalence, bioequivalence and bioavailability, biowaivers.

Received for publication: 11 June 2013.  
Revision received: 2 September 2013.  
Accepted for publication: 20 September 2013.

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Italian Journal of Medicine 2014; 8:80-87  
doi:10.4081/ijm.2014.398

<sup>a</sup> Law no. 149 of 26 July 2005 enforcing legislative decree no. 87 of 27 May 2005 also introduced the term *equivalent medicine* to identify generic drugs. In Article 1bis the generic drug takes on a new and more adequate drug name equivalent: *Article 1-bis. The prescription medicines under Article 7, paragraph 1, of the Leg. Decree no. 347 of 18<sup>th</sup> September 2001, enforced with amendments by Law no. 405 of 16 November 2001, as amended, and Article 1 of this decree-law to the exclusion of those who have enjoyed covers registered patents, are defined as medicinal products equivalent.*

by the Italian Society of Geriatrics and Gerontology in collaboration with the Datanalysis Group, only 30% of our 6 million over 75s are aware of generics, and about 900 thousand actually use them. The others take the branded, more expensive drugs.<sup>4</sup> Furthermore, in our country, physicians tend to prescribe branded rather than generic drugs, thus contributing to increase health-care costs.<sup>5</sup> Despite these problems, the generic segment appears to be the most lively on the Italian drug market with sales volumes on the increase in recent years.<sup>6</sup> According to the *Assogenerici* Association, the obligation to write the active ingredient on the prescriptions has led to an accelerated growth in the sales of equivalent drugs. Recent data show that about 25% more packs were sold last year. The latest OsMed Report<sup>7</sup> confirmed a growth of drugs with expired patents both in terms of spending (+6.4% against 2011) and consumption (+10.2%) in the first nine months of 2012. A Doxa survey on the *care pathways of the future* presented in Milan in October 2013 at the Mario Negri Institute for Pharmacological Research showed that 7 out of 10 Italians are inclined to use generic drugs (73%) and are in favor of their spreading (70%). More importantly, after having tried them, almost 8 out of 10 (77%) reported to have had a positive experience. Nevertheless, Italians tend to privilege branded drugs, which in the first 9 months of 2012 accounted for almost 38.4% of the total expenditure and more than half (55.3%) of the defined daily doses (DDD) consumed per thousand people. The generics represented 25.2% of the total expenditure for drugs with expired patent, almost 10% of total expenditure, and 17.3% of the total drug consumption.

### Need for more information on generic drugs

Generic drugs can provide a less expensive alternative to branded drugs, since they do not require the expensive and long clinical trials needed for innovative medicines. A generic can only be introduced after it is

proven unequivocally that its generic formulation is identical to the brand-name version in terms of active ingredients, efficacy and route of administration.<sup>8</sup> As generic drugs become increasingly available, physicians are asking for more information about the processes implemented to verify that generic versions of brand-name drugs are both safe and effective and offer the same therapeutic results.<sup>9</sup> In order to be licensed by the Authority, a generic medicinal product must meet the same stringent quality standards as the product originator (Table 2).<sup>10</sup> To obtain a marketing authorization, a generic medication must then contain the same active ingredient as the reference product originator and be identical in terms of strengths, pharmaceutical forms (*e.g.* tablets, capsules, liquid, etc.) and route of administration. It must also be bioequivalent to the reference originator, have the same features in terms of identity, strength, purity, quality, be manufactured according to the same high standards foreseen by the rules of good manufacturing practices (GMP) adopted for all medicinal products. Generic drugs are approved on the basis of data deriving from bioequivalence studies. Except for the findings of preclinical and clinical studies, the documents to be submitted for the marketing authorization are the same as those required for the drug originator. Such documents must include pivotal data, administrative data on the authorization holder, summary of product features, package leaflets, labels and packaging format of the medicinal product, description of the manufacturing process, testing of starting materials, control and stability tests on raw materials and final products, dissolution profile with comparisons against the reference originator drug.

### Notions of bioavailability and bioequivalence in generic/equivalent drugs

Drugs are considered to be therapeutic equivalents and suitable for replacement (generic equivalents) if,

#### Table 1. Glossary.

##### Originator drug

Medicinal product taken as reference for the development of a generic product. It is in general (but not necessarily) the first product for which the patent was granted. It generally has a fantasy name, therefore it is also defined as branded medicine.

##### Generic medicinal product

A medicinal product identified by the international non-proprietary name of the active ingredient followed by the name of the Marketing Authorization holder, which is bioequivalent to an already authorized medicinal, and which has the same qualitative and quantitative composition in terms of active substances, the same pharmaceutical form and the same therapeutic indication (unbranded).

##### Drug with expired patent

It's a medication that is no longer covered by a patent or supplementary protection certificate, regardless of whether it is a generic or an originator. Among these drugs, there are both branded and unbranded medicines.

##### List of transparency

In the case of authorized generic medicines and drugs with an expired patent protection refunded by the NHS, the Italian Drug Agency (AIFA) includes both the originator and the generic corresponding drug in a list, called list of transparency, which is updated monthly and available on the AIFA website. This list includes the originators and the corresponding generic drugs together with their reference price. The drugs grouped together in the list of transparency are replaceable.

NHS, National Health Service; AIFA, *Agenzia Italiana del Farmaco*.

among other factors, they are both pharmaceutically equivalent and bioequivalent. The notions of pharmaceutical equivalence, therapeutic equivalence and bioequivalence are slightly different. Pharmaceutical equivalence means that two drug products contain identical amounts of an identical active ingredient in identical dosage forms. A therapeutically equivalent medicinal product should prove to have the same clinical efficacy and safety as the reference product, whose efficacy and safety have been documented with appropriate studies. Instead, it is accepted that a bioequivalence study on the basis of plasma profiles may be an indirect proof of the equivalence of two therapeutic drugs that are pharmaceutically equivalent or pharmaceutical alternatives. Two products are bioequivalent when they generate plasma concentrations similar to those of the active ingredient at which their clinical effects can be expected to be the same.<sup>11,12</sup>

Therefore two products are therapeutically equivalent, when they are both pharmaceutically equivalent and bioequivalent. As a result, the same efficacy and safety profile can be expected when they are administered under the same conditions<sup>11</sup> (Table 3).

### Methods to determine bioequivalence

Generic drug manufacturers must demonstrate that a drug is bioequivalent to its reference drug product.

For this purpose of establishing their bioequivalence, the FDA recommends the adoption of the following methods in order of descending preference: i) pharmacokinetic studies; ii) pharmacodynamic studies (PD); iii) comparative clinical trials; iv) *in vitro* studies.<sup>13</sup> However, one should consider that some of these methods are appropriate only under certain circumstances (*e.g.*, *in vitro* dissolution tests can be used to assess the therapeutic equivalence of highly soluble, rapidly dissolving, orally active drugs), whereas others (comparative clinical and PD studies) are deemed less reliable and are generally recommended only if a pharmacokinetic approach is not possible.<sup>14</sup> Refer to a previous issue of this Journal for a comprehensive review of several topics concerning the concepts of pharmacokinetics, bioavailability and bioequivalence.<sup>15</sup>

### Pharmacokinetic studies

The demonstration of bioequivalence is based on a comparison between the average values of some pharmacokinetic parameters. Bioequivalence studies are based on bioavailability. There are several direct and indirect methods for assessing bioavailability in humans. The parameters to determine the bioavailability of a drug include:

- *Plasma pharmacokinetic (PK) data* (Figure 1):<sup>16</sup> i) time to peak plasma concentration ( $T_{max}$ ); ii) peak

**Table 2. Definition of generic drug.**

Art. 10, par. 5, Leg. Decree 219/2006: A medicinal product which has the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability. The current legal framework based on L.D. 323 - 20/06/96 (converted into Law 425/96) foresees that generics should have *the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the same therapeutic indications*

According to the current European regulations, Article 10.2.b of Directive 2001/83/EC, as amended, states that the various salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, the applicant must provide additional information proving the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance

The composition of the excipients and their appearance can be a source of problems or questions for prescribers: the problem is not insignificant, especially with regard to pharmaceutical forms, such as granules, oral solutions, tablets, capsules, dermatological preparations

### Bioequivalence documentation

According to the EMA guidelines,<sup>10</sup> before granting a MA for a generic drug, the Italian Drug Agency (AIFA) is bound to test the bioequivalence of the generic and the original drug (<http://www.agenziafarmaco.gov.it>). The documentation required to prove that their bioequivalence is below the threshold above which a new drug must be registered does not include tests of bioequivalence with other generics of the same drug already on the market. Bioequivalence studies to be submitted to AIFA in order to obtain a MA for the drug equivalent are based on the comparison of the pharmacokinetic parameters that characterize bioavailability, *i.e.* the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action. The EMA guidelines on how to document bioequivalence indicate the kind of subjects to be involved in the study: healthy volunteers, aged 18-55 years, to reduce variability unrelated to products; both sexes to assess the risk for women of childbearing age; patients if the drug effects or risks are unacceptable for healthy volunteers, genotyping or phenotyping of volunteers may be necessary for reasons related to safety or pharmacokinetics in case of products metabolized by enzymes with genetic polymorphism; in parallel group studies the subjects have to be comparable with respect to the variables that may affect pharmacokinetics, *e.g.* ethnicity, cigarette smoking, metabolic capacity

### Post-marketing safety

Through the pharmacovigilance system set out in Legislative Decree no. 219/2006, art 132 *physicians and other health care professionals are required to report all suspected serious or unexpected adverse reactions which they learn as part of its activities. Even though there all suspected adverse reactions observed, serious, not serious, expected and unexpected from all vaccines and medicines placed under intensive monitoring thus contributing to improve the quality of drugs already the market and the safety of their clients*

EMA, European Medicines Agency; MA, Marketing Authorization; AIFA, *Agenzia Italiana del Farmaco*.

**Table 3. Differences between pharmaceutical equivalence, therapeutic equivalence, bioequivalence and bioavailability.**

| Pharmaceutical equivalence   | Therapeutic equivalence  | Bioequivalence and bioavailability  |
|--|--|---|
| Two drug products contain identical amounts of the identical active drug ingredient in identical dosage forms  | Two pharmaceutically equivalent formulations that proved to be bioequivalent to products that meet the following general criteria:   | Two medicines are bioequivalent if they contain the same active principle and, if, after administration of the same dose under the same conditions, their profiles of concentration / time (bioavailability) are similar to the extent that no significant differences can be identified in terms of efficacy and safety  |
| Two drugs are pharmaceutically equivalent if they: <ul style="list-style-type: none"> <li>- contain the same active principle(s);</li> <li>- have the same dose form and administration route;</li> <li>- are identical in strength or concentration.</li> </ul> These products meet the standards in terms of strength, quality, purity and identity, but may differ in terms of features such as shape, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date, and, within certain limits, labelling | - they are approved as safe and effective; <ul style="list-style-type: none"> <li>- they are pharmaceutical equivalents in that they: i) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and ii) meet compendial or other applicable standards of strength, quality, purity, and identity;</li> <li>- they are bioequivalent in that: i) they do not present a known or potential bioequivalence problem, and they meet an acceptable <i>in vitro</i> standard; or ii) if they do present such a known or potential problem, they have shown to meet an appropriate bioequivalence standard;</li> <li>- they are adequately labelled; and</li> <li>- they are manufactured in compliance with current good manufacturing practice regulations</li> </ul> | Bioequivalence studies are based on bioavailability<br><br><i>Bioavailability</i> is the fraction of the administered dose reaching the systemic circulation. It indicates the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action<br><br><i>Absolute bioavailability</i> is determined by comparing the bioavailability of the active drug in the systemic blood circulation following non-intravenous administration ( <i>i.e.</i> , after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration<br><br><i>Relative bioavailability</i> is determined by comparing the plasma concentration-time-curves (usually as area under the curve) after administration of two different formulations of the same compound ( <i>e.g.</i> , capsule vs tablet vs dissolved in water, etc.) |
| According to the pharmaceutical equivalence of EMA, the pharmaceutical form of test and reference could be different, <i>e.g.</i> tablets vs capsules, vs oral solution  |  |   |

EMA, European Medicines Agency.

plasma concentration ( $C_{max}$ ); iii) area under the concentration/time curve (AUC).

- *Clinical effects.*
- *Urinary data:* i) cumulative amount of drug excreted in the urine (Du); ii) rate of drug urinary excretion (DDU/dT); iii) time of maximum urinary excretion.

The use of urinary excretion data as a surrogate for plasma concentration data may be acceptable in determining the extent of exposure where it is not possible to measure reliably the plasma concentration-time profile of the parent compound. However, the use of urinary data has to be accurately justified if adopted to estimate peak exposure.<sup>10</sup>

Regulatory authorities have stated that differences in systemic drug exposure up to  $\pm 20\%$  are not clinically significant.<sup>17</sup> The  $\pm 20\%$  tolerance range is not related to the active principle contained in the drug, but to the blood concentration. This range refers to the inter- and intra-individual biological variability that applies to the administration of any drug. Hence, one might believe that the appropriate range should be 80-120% ( $100\% \pm 20\%$ ), however that would be incorrect. The symmetrical  $\pm 20\%$  has to be in the log-transformed space for the bioequivalence tests to be valid.

The statistical analysis requires a log-transformation of all concentration-dependent pharmacokinetic measurements, using base 10 or natural logarithms, for clinical, pharmacological and statistical reasons.<sup>18</sup> Logarithmically transformed concentration-dependent PK parameters should be analyzed in accordance with European guidelines (Figure 2).<sup>10</sup>

Two treatments are not considered different from one another, if the 90% confidence interval (CI) of the ratio of a log-transformed exposure measure (AUC and/or  $C_{max}$ ) falls completely within the 80-125% range (but this does not mean that they are *the same!*).<sup>b</sup> The calculated 90% CI should be within 80% and 125%,

<sup>b</sup> Statistically, the parameters of the tested drug are compared to those of the reference medicine [T/R (test/reference)]. Parameters usually considered are the average values of the total AUC and maximum plasma concentration/serum/blood from volunteers healthy post-dose. According to the recommendations, in order to obtain the authorization for a substance not rapidly absorbed, this ratio has to range within a 90% confidence interval 0.8 to 1.25. This means, by giving this generic drug, we can trust that 90 times out of a hundred-the drug will reach a plasma concentration between 80% and 125% of what would be ensured by the reference drug.

proving that the difference in terms of bioavailability is less than 20%. This means that if the 90% confidence interval falls outside the 80-125% range, the two treatments are different (Figure 3).<sup>19</sup> Maintaining a 90% confidence interval among plasma levels within that acceptable range implies that mean plasma concentrations after the administration of the generic do not differ by more than 5-7% from those observed after the administration of the branded product.<sup>20</sup> An internal FDA study conducted between 1996 and 2007 reported that the average differences between generic and innovator drugs were 4.35% for  $C_{max}$  and 3.56% for AUC.<sup>21</sup>

Some authors consider it convenient to distinguish between *bioequivalence* (i.e. 90% CI within the accept-

ance limits), *bioinequivalence* (90% CI completely outside the acceptance limits) and *non-equivalence* (90% CI partly inside and partly outside the acceptance limits). In practical terms, it is necessary to establish inequivalence in order to conclude that a generic is not similar to the reference product, since non-equivalence is inconclusive and another study with more statistical power (i.e. a lower variability or a higher sample size) might be able to conclude equivalence.<sup>22</sup>

### Messages

- Regulatory authorities have stated that differences in systemic drug exposure up to  $\pm 20\%$  are not clinically significant.

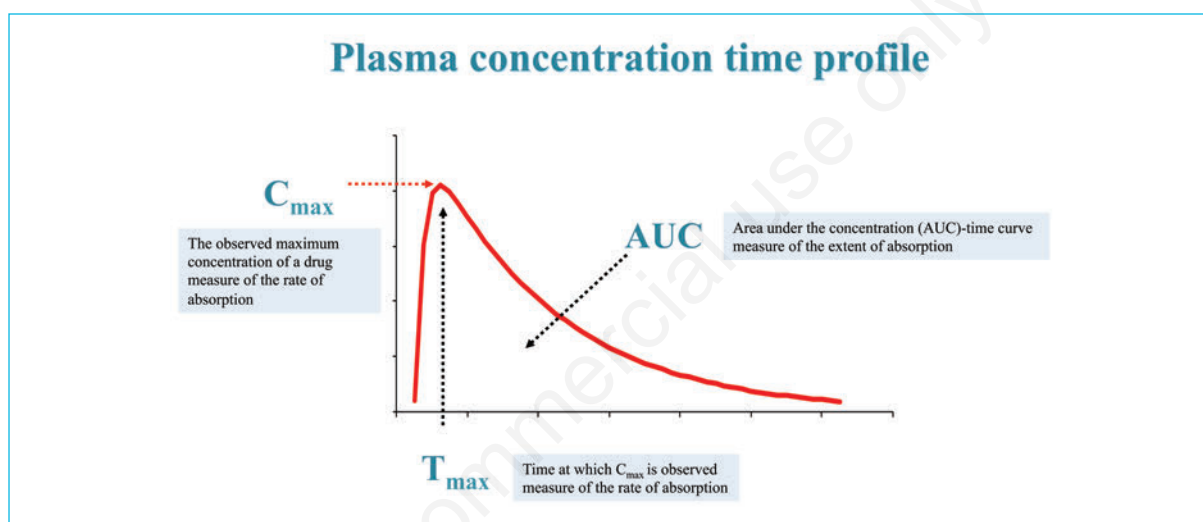


Figure 1. Important pharmacokinetic parameters. Adapted from Gordon, 2012.<sup>16</sup>

- The pharmacokinetic parameters under consideration (e.g.  $AUC_{0-t}$ ,  $C_{max}$  in case of a single dose BE study) should be analyzed using ANOVA.
- The data should be transformed prior to analysis using a logarithmic transformation.
- The terms to be used in the ANOVA model are usually sequence, subject within sequence, period and formulation.
- A statistical evaluation of  $t_{max}$  is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median  $t_{max}$  and its variability between test and reference product.

Figure 2. European Medicines Agency guideline on the investigation of bioequivalence, 2010. Adapted from EMA/CHMP, 2010.<sup>10</sup>

- This range refers to the inter- and intra-individual biological variability that occurs as a result of the administration of any drug.
- The  $\pm 20\%$  tolerance range is not related to the active principle contained in the drug, but to its concentration in the blood.
- The statistical analysis requires a log-transformation of all concentration-dependent pharmacokinetic parameters, using base 10 or natural logarithms, for clinical, pharmacological and statistical reasons.
- 90% CI of the quotients of both the average AUC and  $C_{max}$  of the original drug and its generic fall within the pre-set limit of  $\pm 20\%$ , equivalent to a limit of 0.8 to 1.25 on a logarithmic scale.

To maintain 90% confidence intervals among plasma levels within that acceptable range, mean plasma concentrations after administration of the generic must not differ by more than 5-7% from those observed after administration of the branded product.

### Pharmacodynamic studies

Approaches such as pharmacodynamic bioequivalence testing have been proposed as alternatives to pharmacokinetic bioequivalence studies, but no consensus has been reached on the criteria for PD bioequivalence testing. Hence, there are now various approaches under study.<sup>23</sup> Pharmacodynamic studies are performed for drugs that do not produce measurable concentrations of the parent drug, for drugs with active metabolites in blood or urine, and for those whose bioavailability is not indicative of therapeutic efficacy. The acceptance criteria of equivalence in this

study must be established considering the pharmacological activity of each drug.<sup>24</sup>

### Comparative clinical trials: bioequivalence studies with clinical endpoints

A bioequivalence study with clinical endpoints is a comparative clinical trial in humans that can determine the bioequivalence of dosage forms intended to deliver the same active moiety at an equivalent rate and extent to the site(s) of activity. This approach may be applied to dosage forms intended to deliver the active moiety locally, forms that are not intended to be absorbed, or drug products for which traditional pharmacokinetic studies are not feasible.<sup>25</sup>

### In vitro dissolution testing

The *in vitro* dissolution tests are useful to identify factors that can influence bioavailability, when new drugs are being developed, as well as to perform quality control on production batches.<sup>26</sup> With the introduction of generic drugs, the *in vitro* test has become a useful method to perform assessments prior to the bioequivalence studies, in order to understand the pharmacokinetic pattern with which the active ingredient is released from the formulation and, in special cases, to evaluate the bioequivalence of drugs.<sup>27</sup> In the case of an immediate release solid oral dosage form that is highly soluble in aqueous means (as in the case of a tablet) and of a known and approved active ingredient, pharmacokinetic bioequivalence studies in humans can be avoided. Data obtained from *in vitro* dissolution testing is considered a true surrogate for bioequivalence. When such exception is acknowledged by the regulatory authorities, at the international level

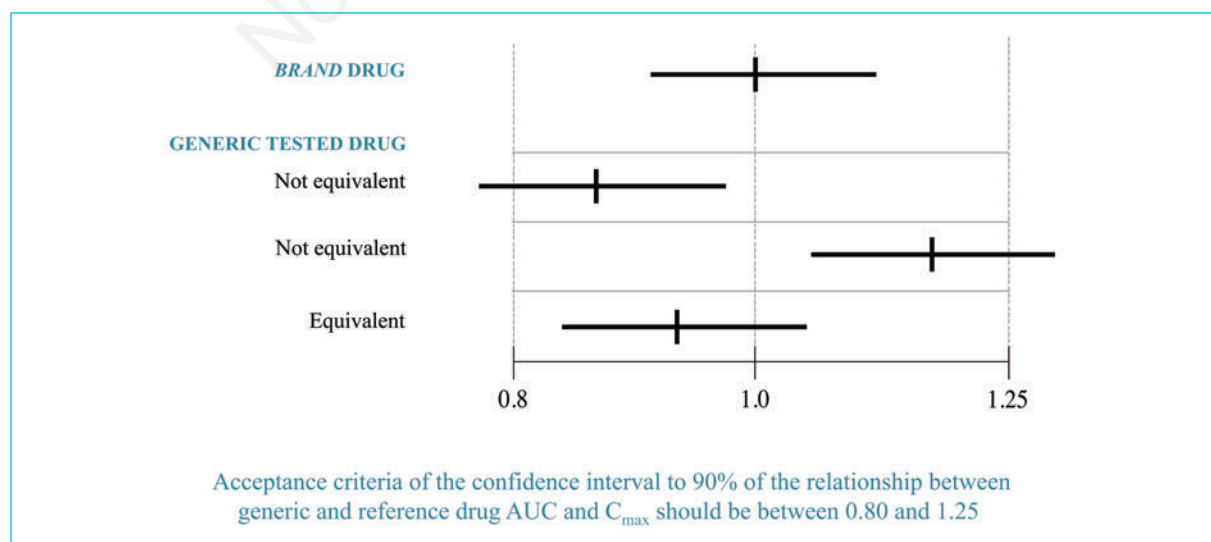


Figure 3. Bioequivalence test. Adapted from SITO, 2011.<sup>19</sup>

the drug in question is takes the name of *biowaiver*<sup>c</sup> (i.e., approved with the exemption of bioequivalence testing in humans).<sup>28-30</sup> The Biopharmaceutics Classification System establishes the criteria to establish which drugs may or may not be exempt from pharmacokinetic bioequivalence studies in humans. This classification groups the pharmacologically active substances into four classes, according to their solubility and intestinal permeability: i) *class 1*, high solubility, high permeability; ii) *class 2*, low solubility, high permeability; iii) *class 3*, high solubility, low permeability; iv) *class 4*, low solubility, low permeability. By combining these properties (solubility and intestinal permeability of the substance) with the dissolution characteristics of the pharmaceutical formulation (ratio concentration/time), we can estimate the key factors that characterize the bioavailability of the drug in terms of speed and extent of absorption or establish whether a tablet can dissolve and release the active substance in an aqueous medium and be absorbed into the bloodstream.<sup>31</sup> Reasons that make *in vitro* studies superior to *in vivo* studies are: i) reduced costs; ii) a more direct assessment of product performance; iii) additional benefits from the ethical point of view.<sup>32</sup>

## Conclusions

Prescribing more generic drugs can lead to cost savings. Their prescribing rates are much lower in Italy than in many other countries. Unfortunately, many misconceptions about generic drugs can still be found not only among patients, but among healthcare providers. Concerns over the therapeutic equivalence between branded products and generics are quite common among physicians. Clinicians need to share a common glossary with the different definitions of equivalent drugs and related regulatory standards. They need to gain further knowledge of the equivalent drugs characteristics, focusing mostly on the concept of bioequivalence and on the related studies. The increase of generic prescribing rates has to become part of overall efforts to improve quality and efficacy for a more sustainable medicine.

<sup>c</sup> A *biowaiver* is defined as the product to be tested (usually in immediate release tablets) identical to the originator or that containing salts with similar properties, provided with: i) high solubility and complete absorption; ii) very high *in vitro* dissolubility; iii) the same (qualitative-quantitative) ingredients of the originator.<sup>25</sup>

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