Generic - equivalent drugs use in internal and general medicine patients: distrust, confusion, lack of certainties or of knowledge? Part 2. Misconceptions, doubts and critical aspects when using generic drugs in the real world

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ABSTRACT

A lot of issues have been raised to argue that equivalent drugs may not work as well or at least the same as what the drug industry likes to call *innovator* products. Many doubts and biases are also reported in connection with the use of generic drugs. Doctors are mostly concerned about their efficacy, their tolerability, the quality and amount of active ingredients, their formulation or excipients, their packaging, their pharmaceutical form and their palatability. We describe the differences between *prescribability* (equivalence when prescribing a drug to a patient for the first time) and *switchability* (interchangeability of drugs for a patient already in treatment) considering the notions of average bioequivalence, population bioequivalence and individual bioequivalence as well as the usefulness of the U.S. Orange Book in the assessment of bioequivalence. Other key issues deserve attention, such as: *duplicate applications* for medicinal products, different salt forms, formulations used in the development of each medicinal product and excipients, product quality. Clinicians in collaboration with pharmacists and research pharmacologists have to find solutions for unanswered questions and unsolved doubts, by developing targeted studies, communication tools and shared guidelines.

Misconceptions among doctors

When it comes to the use of generic drugs, a frequently-asked question is: *Yes, they save us money, but are they good for us*?[1] Both doctors and patients tend to share the same bias that generics differ in quality and therapeutic efficacy from their corresponding brand-name products.[2] The debate is mainly focused on the notion of bioequivalence (BE), how it can be assessed in different groups of people as well as on the notion of intra-subject or inter-subject variability.[3] In Italy, doctors are prevalently concerned about their efficacy (73%), their tolerability (38.4%), their bioequivalence (24.6%), the quality of the active ingredients (22.6%), their formulation or excipients (19.5%), the amount of the active ingredients (15%), their package (10%), their pharmaceutical form (3.7%), and their palatability (2.2%).[4] In their review, Ferner et al pointed out a lot of reasons to expect that generic drugs may not work as well or at least the same as what the drug industry likes to call *innovator* products.[5] Some doubts, biases and questions associated with the use generic drugs are reported in Table 1.

Full clinical trials are not required to approve generics

According to the guidelines of the World Health Organization (WHO), 18 to 24 healthy adult volunteers are considered sufficient for a bioequivalence study. The number of participants can be higher, if the absorption or clearance of the drug is highly variable. In the studies designed to test the bioequivalence of oral formulations, in order to minimize the extent of the inter-individual variability and reduce the likelihood of errors caused by the interaction between dis-

ease and concomitant conditions or the drugs or the differences in formulation, volunteers are not allowed to smoke or take medications and have to eat standardized meals to exclude that the co-administration with food can affect the generic drug under study.[6,7] In order to further minimize the effects of non drug-related variation, bioequivalence studies are typically based on a crossover design. Half of the subjects receive the test drug first, followed by the brand-name product, with a washout period in between, while the other half receives the drugs in the reverse order. The inversion of the groups (*crossover*) is useful to limit individual variability.[8] In the assessment of bioequivalence, studies comparing the results of generics and brand-name products showed that the quality of reporting in these trials needs some improvement.[9] According to some experts, the development of a drug equivalent should not only be based on bioavailability studies, but also on therapeutic bioequivalence assessments to confirm its clinical efficacy, which cannot be inferred from a mere comparison of the plasma concentrations of the drugs.[10] However, despite generic prescribing offers unquestionable economic benefits, controlled clinical data from studies on the use of these drugs in patients with cardiovascular diseases compared with healthy volunteers is limited. In patients with cardiovascular disease, the risks of mortality, bleeding and drug discontinuation and the incidence of adverse events were not different between groups treated either with branded or generic clopidogrel.[11] Therefore, a remarkable role can be played by meta-analyses, as can be seen in the meta-analysis on 47 studies on the clinical effects of cardiovascular drugs compared to equivalent originators. In this systematic review and meta-analysis, clinical equivalence was confirmed in 7 out of 7 randomized controlled trials (RCTs) (100%) on β-blockers, 10 out of 11 RCTs (91%) on diuretics, 5 out 7 RCTs (71%) on calcium channel blockers, 3 out of 3 RCTs (100%) on antiplatelet agents, 2 out 2 RCTs (100%) on statins, 1 out of 1 RCT (100%) on angiotensin-converting enzyme inhibitors, and 1 out of 1 RCT (100%) of α-blockers. Among narrow therapeutic index drugs, clinical equivalence was reported in 1 out of 1 RCT (100%) on class 1 antiarrhythmic agents and 5 out of 5 RCTs (100%) on warfarin.[12] Some studies comparing the bioequivalence of generic and innovator drugs that were conducted on orally administered generic drug products approved by the Food and Drug Administration (FDA) from 1996 to 2007 (12 years) showed that the area under the curve (AUC) of the generic product differed from that of the innovator product by less than 10%.[13]

Drug interchangeability: *prescribability* and *switchability*

There is a difference between *prescribability* (equivalence when prescribing a drug to a patient for the first time) and *switchability* (interchangeability of drugs in patients already in treatment within a a clinical setting in which a practitioner transfers a patient from one drug product to another.[14] *Prescribability* refers to the choice of the physician between either the brand-name drug or its generic copy when prescribing an appropriate drug to his/her patients. In its 2001 guideline, the U.S. FDA recommended that also population bioequivalence and individual bioequivalence (IBE) be assessed to gain a better understanding of prescribability and switchability between a brand-name drug product and its new formulation or generic copy.[15] As to IBE, the FDA recommended the use of a 2×4 crossover design and the statistical test procedure proposed by Hyslop *et al*.[16] The concepts of prescribability and switchability highlight the difference between a approached based on population bioequivalence and approached base on individual bioequivalence. In fact two formulations may be considered *bioequivalent for a population,* if, in addition to the bioavailability average value, their distributions

Table 1. Biases, doubts and critical aspects associated with the use of generic drugs.

1. *Full clinical trials are not required* to approve generics - that's why they are so inexpensive, after all, - so true clinical equivalence is never tested

2. *Drug interchangeability:* concepts of *prescribability* and *switchability*

   Intra-patient variability

3. Bioequivalence between *generics drugs: the bio-creep phenomenon*

4. Bioequivalence and *different salt forms*

5. *Different indications* between branded and equivalent drugs

6. Medication copies as *duplicate application* for medicinal products

7. Generic drugs may use different formulations and *excipients*: which consequences?

8. *Modified-release formulations*

9. *Poor quality* of products, not complying with the criteria of *good manufacturing practices*

10. *Pharmacies constantly change* the generic version they purchase depending on where they can get the best price

around the means are sufficiently similar. The AUC or C_{max} of the two formulations can have a sufficiently similar average value and at the same time a significantly different variance. In this case, the two formulations are not equivalent for a population, because the bioavailability distributions are significantly different. Demonstrating population bioequivalence is of significant importance, as it can enable a physician who is prescribing a new treatment with a generic drug rather than the corresponding branded product to expect an average

equivalent therapeutic outcome in the population of his patients (Table 2, Figure 1).[17-19]

Demonstrating population BE is of significant importance, as a physician can expect a reasonable average equivalent therapeutic result in the population of his/her patients, when prescribing a new treatment with a generic equivalent drug rather than its corresponding brand-name product. Population bioequivalence, however, does not provide any information about the likelihood of having an equivalent response to two

Table 2. Types of bioequivalence: average, population and individual bioequivalence.

ABE	PBE	IBE
Current regulatory requirement	**Prescribability**	**Switchability**
• It addresses only the mean (center of distribution), but not the variability (shape of distribution) • It does not address switchability	PBE Refers to the clinical setting in which a practitioner: • Prescribes a drug product to a patient for the first time • He has no information on his patient • The prescriber needs to know the comparability of the 2 or n formulations in the population (population bioequivalence);	• IBE takes into account intra-subject and subject-by-formulation variances, being • A relevant criterion to manage changes in treatment, when a reference drug is replaced with 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
▪ Bioequivalence is confirmed, if the average bioavailability of the test product is within ±20% of that of the reference product with 90% assurance (raw data), or ▪ Bioequivalence is claimed, if the ratio of average bioavailabilities between test and reference products is within (80%, 125%) with 90% assurance (log-transformed data)	PBE takes into account inter-subject variability (inter-subject variance) and therefore interchangeability for a patient who needs to start a treatment.	*Test* and *reference* are bioequivalent if the individual subject means and variabilities are sufficiently similar in terms of AUC and C_{max}
ABE may not be sufficient to ensure that an individual patient could be switched from a reference to a generic formulation (*e.g.,* more than 50% of subjects may be outside the BE range when the average BE is actually proven)	If two drugs A an B are equivalent at the population level, the replacement of a drug with another in the whole population does not involve any difference in the average. Stating a PBE for a new patient who has to start a therapy means that he/she can be put either on drug A or B	

ABE, average bioequivalence; PBE, population bioequivalence; IBE, individual bioequivalence; BE, bioequivalence; AUC, area under the concentration. *Modified from Chow, 2003*[17] *and Chow* et al., *2011.*[18]
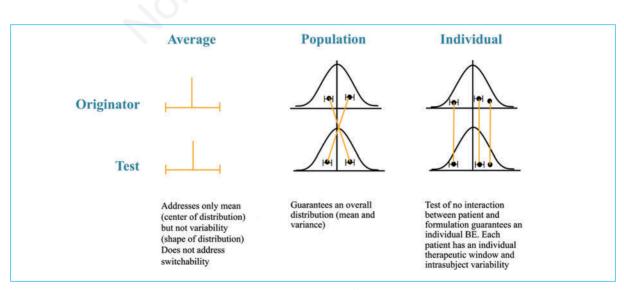

Figure 1. Types of bioequivalence (BE). *Adapted from Toutain, 2008.*[19]

formulations in an individual patient. Bioequivalence tests do not give any information about intra-patient variability, *i.e.* the differences in pharmacokinetics that can occur in the same patient from one dose to the next during the course of treatment.[20] In order to gain this understanding, it is necessary to estimate IBE, *i.e.* bioequivalence associated with the individual subject in order to assess what percentage of individual subjects respond in an equivalent manner to the prescription of the generic and the corresponding innovator product. The assessment of individual bioequivalence is intended to confirm that an individual could be switched from the reference product to the test product with unchanged efficacy and safety. IBE considers similar effects of both drugs on the same individual. It takes into account intra-subject and subject-by-formulation variances and is a relevant indicator to manage changes in treatment, when a reference drug is substituted for its generic counterpart.[21] IBE also allows a more accurate assessment of bioequivalence in drugs with high pharmacokinetic variability and narrow or large therapeutic range.[3,22] The most important implication of individual bioequivalence is that products deemed bioequivalent can be used interchangeably in the target population (switchability).[23] For some drug products, individual bioequivalence offers several advantages compared with the mere use of averages, since it allows to compare intraindividual variances, adjust the bioequivalence parameter to the reference variability and detect any potential significant subject-by-formulation interaction. In order to analyze IBE, the generic and brand products must be administered twice to the same group of subjects. The FDA recommends replicate study designs for modified-release dosage forms and highly variable drug products and also encourages the inclusion of a heterogeneous population of volunteers in bioequivalence studies.[24] Individual bioavailability becomes, therefore, a fundamental parameter to replace one formulation with another over the course of treatment without affecting its original safety and therapeutic profile. The FDA also considers a new IBE standard, whereby the subject would receive a dose of the brand name drug two times. The two concentration-time curves, which reflect average bioavailability, intra-subject variability and lot-to-lot variation, would be the *goalposts* within which the generic formulation must fall.[25] While average and population bioequivalence can be assessed in two-period (non-replicated) crossover studies, individual bioequivalence requires three- or four-period replicated studies, with a preference for four-period studies.[26]

Messages

- *Individual bioavailability becomes, therefore, a fundamental parameter to replace one formulation with another over the course of treatment without affecting its original safety and therapeutic profile.*

- *When the bioequivalence of test and reference drugs is correctly demonstrated, also their activity and safety can be expected to be equivalent.*[27]

Bioequivalence between *generic drugs*: the *bio-creep* phenomenon

There is a difference between brand-generic and generic-generic substitution. The concept of bioequivalence does not foresee the transitive property and does not allow us to state that two products, each one bioequivalent to the same reference drug, can be considered bioequivalent to each other. In fact, tests on bioequivalence are made between an individual generic product and its corresponding branded product, but not between two generics. As a result, there is no proof that two or more generics of the same branded product can be considered bioequivalent to each other and therefore are fully interchangeable (phenomenon of *bio-creep*). For example, if we take a generic with a bioavailability (AUC) of +15% and another generic with a bioavailability –15%, they are both bioequivalent with respect to the standard that they mimic, but are not bioequivalent to each other. According to the regulations, a generic drug can be used as a *substitute* for the corresponding brand-name drug, if it proved bioequivalent to it. Current regulations do not indicate that two generic copies of the same brand-name drug can be used *interchangeably*, even though they are bioequivalent to the same brand-name drug. Bioequivalence between generic copies of a brand-name drug is *not* required.

Message

Current regulations do not indicate that two generic copies of the same brand-name drug can be used interchangeably*, even though they are bioequivalent to the same brand-name drug.*

Food and Drug Administration *Orange Book*

In May 2007, the FDA released a document entitled *Critical Path Opportunities for Generic Drugs* that addressed some specific challenges in the development of generic drugs. The key steps in generic product development are typically as follows: characterization of the reference product, design of a pharmaceutically equivalent and bioequivalent product, design of a consistent manufacturing process and completion of a pivotal bioequivalence study.[28] Subsequently the FDA implemented a number of specific paths to recognize therapeutic equivalence. Once approved by the FDA, a generic product is assigned a therapeutic rating and listed in the list of Approved Drug Products with Therapeutic Equivalence Evaluation (also known as Orange Book).[29] The Orange Book is periodically updated and

Table 3. Food and Drug Administration therapeutic equivalence codes.[29]

AA	Products in conventional dosage forms not presenting bioequivalence problems
AB	Products meeting necessary bioequivalence requirements
AN	Solutions and powders for aerosolization
AO	Injectable oil solutions
AP	Injectable aqueous solutions and, in certain instances, intravenous nonaqueous solutions
B	Drug products that the FDA, at present, considers not to be therapeutically equivalent to other pharmaceutically equivalent drug products
BC	Extended release dosage forms (capsules, injectables, and tablets)
BD	Active ingredients and dosage forms with documented bioequivalence problems
BE	Delayed-release oral dosage forms
BN	Products in aerosol-nebulizer drug delivery systems
BP	Active ingredients and dosage forms with potential bioequivalence problems
BR	Suppositories or enemas that deliver drugs for systemic absorption
BS	Products having drug standard deficiencies
BT	Topical products with bioequivalence issues
BX	Drug products for which data are insufficient to determine therapeutic equivalence

FDA, Food and Drug Administration.

includes all the bioequivalence studies, indicating for each drug equivalent its interchangeability with other products. It has been conceived to promote the penetration and the use of generic drugs on the market and at the same time to protect the interests of patent holders of brand-name drugs as well as patients.[30] The coding system for the therapeutic equivalence evaluations is designed to allow users to determine quickly whether the Agency considers a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). The two basic categories in which multisource drugs have been placed are indicated by the first letter as follows: code A or B indicates whether a drug will produce the same clinical effects and carry the same risk of adverse events when given to patients under the conditions specified in the labeling. Therefore, the first letter provides essential information about the potential substitutability of a drug. The second letter (A, B, C, D, E, N, O, P, R, S, T, or X) of the therapeutic equivalence code provides information about the dosage form and, in some cases, the results of the FDA's evaluation of actual or potential bioequivalence problems. The second letter also enables pharmacists to rapidly assess whether a proposed substitute has the same route of administration at the same dosage as the drug prescribed originally. It may also inform about any pharmacokinetic and pharmacodynamic study conducted to address bioequivalence issues. The two basic categories into which multisource drugs are classified are indicated by the first letter as follows (FDA therapeutic equivalence codes)[31] (Table 3).[29]

A=Substitutable

Drug products that the FDA considers to be *therapeutically equivalent*[a] to other pharmaceutically equivalent products, *i.e.*, drug products for which:[29] i) there are no known or suspected bioequivalence problems. These are designated as AA, AN, AO, AP, or AT,

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[a] *Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. FDA classifies as therapeutically equivalent those products that meet the following general criteria: i) they are approved as safe and effective; ii) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; iii) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in* vitro *standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; iv) they are adequately labeled; v) they are manufactured in compliance with current good manufacturing practice regulations. The concept of therapeutic equivalence, as used to develop the List, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., ibuprofen* vs *naproxen for the treatment of pain). Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single*

depending on the dosage form; or ii) actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. These are designated AB.

B=Inequivalent, NOT Substitutable

Drug products that at this time the FDA considers NOT to be therapeutically equivalent to other pharmaceutically equivalent products, *i.e.*, drug products for which actual or potential bioequivalence problems have not yet been resolved by adequate evidence of bioequivalence. This problem often occurs with specific dosage forms rather than with active ingredients.

No such system for the evaluation of bioequivalence is available either in Italy or in Europe.

Bioequivalence and different salt forms

Salification of an active ingredient can substantially change the properties of dissolution, absorption and efficacy of a pharmaceutical preparation.[32] The current legal provisions foresee that *different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of active substances are considered the same active substance, if they do not show significantly different properties in terms of safety and/or efficacy...* (art. 10, subsection 5 b, D.lgs. 219/2006). Pharmaceutical alternatives[b] are intended as drugs with *therapeutic equivalence*, having the same therapeutic moiety, but different salts, esters or complexes.[33] A much debated issue is the possibility that different salts of the same active ingredient may exhibit different chemical-physical and pharmacological properties, potentially leading to differences in their profile of efficacy and/or tolerability, with potential strategies to incorporate different salts of a recognized laboratory active pharmaceutical ingredient in a brand company's marketed dosage form, challenging the regulatory authorities to approve bioequivalent products.[34] However, there are no reliable methods to predict accurately the pharmacological consequences associated with changes of the salt form of an active ingredient. The literature reports some examples of different salt forms which differ both in terms of absorption rate, pharmacodynamic and toxicity profile of the same active ingredient.[35] Pharmaceutical salts are somewhere considered not chemically equivalent, since such chemical differences may result into differences in therapeutic efficacy.[36] The salification process makes it possible to change the properties of a chemical-biological active ingredient without changing its original structure. In so doing, it is possible to vary its kinetics, absorption and physico-chemical properties (stability, hygroscopicity, dissolution). It is important to highlight that different salts of the same active ingredient are separate products, characterized by a biological and chemical profile, whose effects cannot be predicted with certainty when referring to an active standard. Therefore, it is fundamentally wrong to think that two different forms of the same salts for the active substance act, in terms of therapeutic efficacy and toxicity, in an identical manner. Consequently, due to this lack of certainty, interchangeability of generic and innovator drugs remains controversial and may undermine the response and/or safety of patients. An example is provided by the case of amlodipine which raised conflicting opinions in the literature.[37,38] Salt-joining makes a hydrophobic molecule hydrophilic; thus improving, especially in psychoactive drugs, kinetics, absorption, or physico-chemical properties (*e.g.*, stability, hygroscopicity, fluidity).[32] This may explain differences between generic and brand-name amitriptyline, nortriptyline, desipramine, and trimipramine.[39] In order to avoid problems, physicians should prescribe generics containing the same salt as their brand-name counterparts.[40]

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source or coded as non-equivalent (e.g., BN). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications. FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ for other features such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product[29] *(Orange Book Preface, ...).*

[b] *Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standards of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates[33] (Federal Register, 1997).

Messages

- *It is fundamentally wrong to think that two different forms of the same salts for the active substance act, in terms of therapeutic efficacy and toxicity, in an identical manner.*
- *In order to avoid problems, physicians should prescribe generics containing the same salt as their brand-name counterparts.*

The example of clopidogrel

Many active substances are formulated as salts to improve their solubility in aqueous solutions and in the gastrointestinal tract. Some generic clopidogrel products have this salt preparation, while others are compounded like, for example, clopidogrel hydrochloride, clopidogrel besylate, or clopidogrel freebase. Therefore one would wonder whether these different salt preparations act differently on their target receptors. According to some opinions, different clopidogrel salts exhibit the same pharmacodynamic properties: they all dissociate in the gastrointestinal tract before reaching the blood circulation.[41] The European Medicines Agency adopted positive opinions for 13 generic forms of three different salts of clopidogrel: hydrogen sulphate (two), besylate (four) and hydrochloride (seven).[42] In a comparison between the original clopidogrel bisulfate and the generic clopidogrel bisulfate administered to patients with coronary stents, the replacement showed a comparable inhibition of ADP-induced platelet aggregation. However, the decision to introduce generic clopidogrel might be based on the analysis of platelet function, clinical risk factor, and lesion complexity and requires caution on the part of physicians, when routinely introducing generic clopidogrel bisulfate.[43] In a study designed to compare the effect of original clopidogrel (clopidogrel bisulphate) to equivalent clopidogrel preparations (clopidogrel hydrochloride and clopidogrel besylate) and prasugrel on platelet reactivity in patients with coronary artery disease, generic preparations provided similar inhibition of platelet reactivity to original clopidogrel bisulphate, although prasugrel was more efficient.[44] Other studies showed equal efficacy of both brand and generic clopidogrel in reducing platelet aggregation.[45,46] This data contrasts with a descriptive laboratory analysis of a platelet reactivity assessment in 1579 patients (1111 men and 468 women, 71.7±11.7 years of age) with acute coronary syndrome. Their platelet reactivity was significantly higher in clopidogrel base (generic preparation), than clopidogrel hydrogen sulfate, thus emphasizing the need for accurate post-marketing surveillance on generic forms.[47] A recent editorial on the use of generic clopidogrel argues that: ... *on balance, a transition to generic clopidogrel is reasonable and probably inevitable. Because no robust system currently exists for tracking and circulating outcomes with generic clopidogrel, clinicians should be vigilant for adverse events and aggressive in reporting ...* This applies mostly in case of adverse outcomes, including stent thrombosis, also considering the possibility of an increased risk when the variability related to the drug formulation adds to the preexisting variability in patient response.[48]

Different indications between branded and equivalent drugs

Some other aspects need careful consideration before opting for any prescription/replacement of therapy. Referring back to the example of clopidogrel, another critical issue concerning its *equivalent drug introduction* is represented by the lack of uniformity in the therapeutic indications, since some technical sheets of generics do not report all indications.[49] In some cases the original branded drugs, authorized on the basis of preclinical studies and RCTs, might not have the same indications as their corresponding generic drugs, containing the same active ingredient. Therefore indications can differ and most often are more limited for generics (Table 4).[50] In these situations, as was already clarified, a prescription of a medicinal product in place of another is not off-label, because the substitution of an originator with its generic is based on the documentation of bioequivalence and not on the RCTs that led to the recognition of the drug originator.[51]

Message

The prescription of a medicinal product in place of another does is not off-label, because the substitution of an originator with its generic is based on the documentation of bioequivalence and not on the RCTs that led to the recognition of the drug originator.

Table 4. Different indications between branded and equivalent drug: clopidogrel.

Originator	Equivalent drug
Prevention of atherothrombotic events in patients with myocardial infarction, stroke and established peripheral ischemic artery disease	All equivalent drugs have the same indication as the originator
Prevention of atherothrombotic events in association with acetylsalicylic acid, in patients with acute coronary syndrome with or without ST-segment elevation	Lacking indication

Modified from Cordella et al.*, 2011.*[50]

Medication copies as *duplicate application* for a medicinal product

In Italy, before the introduction of patent protections, companies were free to copy, register and market medicines copied from *the legitimate* owners of a patent not recognized in Italy. The registration *copy* or *duplicate application* for a medicinal product, as required by the European legislation, refers to the originator which is linked to the same dossiers and the same legal basis, but has a different brand. In short, a company could copy and market the drug registered with an invented name, but without producing any documentation certifying its bioequivalence to the originator.[52]

Generic drugs may use different formulations and *excipients*: which are the consequences?

Many of the doubts over the efficacy of generic drugs as opposed to the original products are related to their excipients. These suspicions are not justified by the definition of *excipients* as inert, *neutral* (pharmacologically inactive) ingredients of a medicine, *i.e.* substances with no biological activity. These substances are used in the formulations to modify the absorption rate and therefore, to some degree, the duration of action of a medicine. Generic excipients have to be previously used for approved drugs for which there is evidence that they have not affected their safety or efficacy.[53] Excipients, which include preservatives, stabilisers, coloring agents, sweeteners, and aromatics can lead to different absorption properties or adverse reactions.[54] Pharmaceutical excipients used for oral dosage forms have been traditionally considered inert. However, recent experience and new results have shown that they can interact with the active drug ingredient, affecting its dissolution, absorption and bioavailability.[55] Many *inert* excipients may produce subtle changes that could directly or indirectly alter the activity of membrane-spanning proteins, such as transporters. The formulations used in the development and production of each medicinal product can affect bioavailability and turn crucial for the purpose of bioequivalence, no matter whether this is due to the physico-technological of the active principle, the quantity of excipients in the composition or the manufacturing process. This concept is particularly important for the solid forms of medicinal products for oral administration. For example, a change in the particle size of the assets rather than in the percentage content or nature of the excipients, in particular of disintegrants, binders, lubricants and surfactants, can also lead to remarkable differences in terms of bioavailability.[52] An example is the case of nimesulide, for which some generic formulations could not be re-garded as therapeutically equivalent to the reference preparation.[56] In this way, excipients could alter the overall absorption, distribution, metabolism, excretion and toxicity properties.[57] Equivalent medicines do not necessarily need to contain the same excipients as the original medicine. We have to ensure that the active ingredient release profile of the equivalent medicine matches that of the original medicine, as confirmed by the proof of bioequivalence.

Messages

- *Equivalent medicines do not necessarily need to contain the same excipients as the original medicine.*
- *The release profile of the active ingredient from the equivalent medicine matches that of original medicine, as confirmed by the proof of bioequivalence.*
- *In some cases, excipients can lead to different absorption properties of a drug, affecting its dissolution, absorption and bioavailability.*
- *We have to ensure that the release profile of the active ingredient of the equivalent medicine matches that of the original medicine, as confirmed by the proof of bioequivalence.*

Modified-release formulations

Modified release (MR) dosage forms are formulations with a rate and/or site of release of the active pharmaceutical ingredient is different from that of the conventional immediate release dosage forms administered through the same route. This deliberate modification is achieved using a special formulation design and/or a different manufacturing method. These formulations may have a prolonged release, a delayed release, a biphasic release or a pulsatile release. Problems may also occur with generics in MR formulations, which may not have the same pharmacokinetic profiles as their brand-named counterparts. The British National Formulary advised that prescriptions for modified-release diltiazem hydrochloride, nifedipine, and theophylline be filled with the brand-name drug only.[58] Morever, a recent study concluded that 2 modified-release products of methylphenidate and nifedipine had concentration profiles that strongly diverged during the period of absorption, although the formulations met the regulatory criteria for bioequivalence.[59]

Poor quality of products not complying with the criteria of *good manufacturing practices*

The difference against the branded product may also be related to the quality of raw materials used to manufacture generics, even though they must meet the same legal requirements in terms of raw materials and good manufacturing practices (GMP). However, the

attempt to lower prices excessively can lead to choose lower prices excessively can lead to choose lower quality and less purified raw materials and less reliable active substances with a far poorer quality control. GMPs are the basis for maintaining bioequivalence. The law does not require to retest a generic product once the quality criteria are met, but in some cases, when doubts arise about product quality, retesting and controls become mandatory. In a study on the pharmaceutical properties of carvedilol, the brand was compared with generic products (tablets of 6.25-12.5-25 mg); 35 generic formulations, produced by 20 companies, sold in 19 countries were analyzed. The results of the study showed that the quantity of the active substance was not correct (n=3), there were excessive impurities (n=1), hardness did not comply with the standard (n=11), the *in vitro* dissolution profile was not equivalent (n=9).[60] Unfortunately it is not easy to make these inspections in remote countries such as India and China.[61]

Do *pharmacies frequently change* the generic version they purchase, depending on where they can get the best price?

The ability to replace an equivalent drug with another can encourage the use of generic medicines. In accordance with the Italian law, *if the physician does not indicate on the prescription that the prescribed drug is not replaceable, the pharmacist is bound to inform the patient and, unless otherwise requested, must give him/her the cheapest drug available on the market* [L. 24/03/2012 no. 27, G.U. no. 71, 24/03/2012, Suppl. Ord. no. 53 (art. 11, par. 12). Available from: http://www.altalex.com/ index.php?idnot=17421]. Do physicians and pharmacists accurately inform patients about equivalent drugs? A survey showed that the pharmacists inform the patient about the availability of generics only in 25% of the cases.[62]

Conclusions

Many biases, doubts and critical aspects associated with the use of generic drugs may affect the decision-making process of physicians. Some are described in our paper, but many others could be further explored in specialized settings of clinical pharmacology. Open questions on bioequivalence, which have not yet been clearly resolved by recommendations and require tailored protocols, concern drugs with a wide acceptable pharmaceutical titre, drugs with a high variability, drugs with prevalent active metabolites, endogenous substances (*e.g.* cholecalciferol),[63] drugs cleared with long half-lives, drugs that cannot be administered to healthy volunteers and drugs with multiple peak phenomena.[27,64] Generic drugs provide an excellent op-

portunity for an economically sustainable medicine. Clinicians, together with pharmacists and research pharmacologists have to find solutions for unresolved questions and unsolved doubts by targeted studies, communication tools and shared guidelines.

References

1. Kamerow D. The pros and cons of generic drugs. BMJ 2011;343:d4584.
2. Paveliu MS, Bengea S, Paveliu FS. Generic substitution issues: brand-generic substitution, generic-generic substitution, and generic substitution of Narrow Therapeutic Index (NTI)/critical dose drugs. Maedica 2011;6:52-8.
3. Meredith P. Bioequivalence and other unresolved issues in generic drug substitution. Clin Ther 2003;25:2875-90.
4. Sextantfarma. I farmaci equivalenti: attualità e prospettive; 2009. Available from: http://www.sextantfarma.it/template.php?pag=40828
5. Ferner R, Lenney W, Marriott J. Controversy over generic substitution. BMJ 2010;340:c2548.
6. Food and Drug Administration, Center for Research. Guidance for industry: bioavailability and bioequivalence studies for orally administered drug products -general considerations; 2003. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf
7. World Health Organization. Multi-source pharmaceutical products: WHO guideline on registration requirements to establish interchangeability. WHO Technical Support Series no. 863. Geneva: WHO; 1996.
8. Meyer MC. Generic drug product equivalence: current status. Am J Manag Care 1998;4:1183-9.
9. van der Meersch A, Dechartres A, Ravaud P. Quality of reporting of bioequivalence trials comparing generic to brand name drugs: a methodological systematic review. PLoS One 2011;6:e23611.
10. Corsini A. Equivalenti: considerazioni di farmacologia. Giorn Ital Farmacoecon Farmacoutil 2013;1:15-20.
11. Caldeira D, Fernandes RM, Costa J, et al. Branded vs. generic clopidogrel in cardiovascular diseases: a systematic review. J Cardiovasc Pharmacol 2012;61:277-82.
12. Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA 2008;300:2514-26.
13. Davit BM, Nwakama PE, Buehler GJ, et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Ann Pharmacother 2009;43:1583-97.
14. Masiero L, Traversa L. Alcune criticità nella valutazione della bioequivalenza. BIF 2008;XV:123-9.
15. Food and Drug Administration. Guidance for industry on statistical approaches to establishing bioequivalence. Rockville, MD: Center for Drug Evaluation and Research, Food and Drug Administration; 2001.
16. Hyslop T, Hsuan F, Holder DJ, A small sample confidence interval approach to assess individual bioequivalence. Statist. Medicine 2000;19:2885-97.
17. Chow SC. Statistical methods for assessment of individual/population bioequivalence. Boston; 2003. Available from: http://www.powershow.com/view/cf6c3-MjEyZ/Statistical_Methods_for_Assessment_of_Individu-

alPopulation_Bioequivalence_SheinChung_Chow_PhD_Bio_powerpoint_ppt_presentation

18. Chow SC, Endrenyi L, Chi E, et al. Statistical issues in bioavailability/bioequivalence studies. J Bioequiv Availab 2011;3:1-8.

19. Toutain PL. Bioequivalence some challenges and issues - Informal CVMP/CMDv. Paris; 2008. Available from: http://physiologie.envt.fr/spip/IMG/ppt/final_Bioequivalence_web_CVMP_paris_2008.ppt

20. Balthasar J. Bioequivalence and bioequivalency testing. Am J Pharm Educ 1999;63:194-8.

21. Lopes N, Ruas K, Serra CHdR, Porta V. Average, population and individual bioequivalence: answering questions on drug interchangeability. SA Pharmaceutical J 2010;77:46-8.

22. Endrenyi L, Midha KK. Individual bioequivalence - has it time come? Eur J Pharm Sci 1998;6:271-7.

23. Chen ML, Patnaik R, Hauck WW, et al. An individual bioequivalence criterion: regulatory considerations. Stat Med 2000;19:2821-42.

24. Chen ML, Lesko LJ. Individual bioequivalence revisited. Clin Pharmacokinet 2001;40:701-6.

25. Williams RL, for Center for Drug Evaluation and Research. Therapeutic equivalence of generic drugs: response to National Association of Boards of Pharmacy; April 16, 1997. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm073224.htm

26. Wijnand HP. Assessment of average, population and individual bioequivalence in two- and four-period crossover studies. Computer Methods Progr Biomed 2003;70:21-35.

27. Marzo A, Porro E, Barassi A. Generic drugs: myths, facts, and limitations. Ital J Med 2012;6:146-52.

28. Lionberger RA. FDA critical path initiatives: opportunities for generic drug development. AAPS J 2008;10:103-9.

29. Food And Drug Administration. The Orange Book: approved drug products with therapeutic equivalence evaluations. 34th Ed. Silver Spring, MD: Food And Drug Administration; 2014. Available from: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

30. Gruppo di Studio SIF sui Medicinali Equivalenti. Farmaci equivalenti - Position paper. Milano: Società Italiana di Farmacologia (SIF); 2010. Available from: http://www.sifweb.org/docs/sif_position_paper_farmaci_equivalenti_ott2010.php

31. Henderson JD, Esham RH. Generic substitution: issues for problematic drugs. South Med J 2001;94:16-21.

32. Brunello N, Racagni G. Sali diversi sono farmaci diversi? Effetti della salificazione sulle proprietà farmacodinamiche, farmacocinetiche e cliniche di un farmaco. Facts News Views 2003;4:1-4.

33. Federal Register, Drug Products. Bioequivalence requirements and in vivo bioavailability procedures. Federal Register 1997;62:1634-5. Available from: https://www.federalregister.gov/

34. Verbeeck RK, Kanfer I, Walker RB. Generic substitution: the use of medicinal products containing different salts and implications for safety and efficacy. Eur J Pharm Sci 2006;28:1-6.

35. Davies G. Changing the salt, changing the drug. Pharm J 2001;266:322-3.

36. Patel A, Jones SA, Ferro A, Patel N. Pharmaceutical salts: a formulation trick or a clinical conundrum? Br J Cardiol 2009;16:281-6.

37. Meredith PA, Potential concerns about generic substitution: bioequivalence versus therapeutic equivalence of different amlodipine salt forms. Curr Med Res Opin 2009;25:2179-89.

38. Mignini F, Tomassoni D, Traini E, Amenta F. Single-dose, randomized, crossover bioequivalence study of amlodipine maleate versus amlodipine besylate in healthy volunteers. Clin Exp Hypertens 2007;29:539-52.

39. Meredith PA. Generic drugs. Therapeutic equivalence. Drug Saf 1996;15:233-42.

40. Lewek P, Kardas P. Generic drugs: the benefits and risks of making the switch. Family Practice 2010;59:634-40.

41. Baumgärtel C. Generic clopidogrel-the medicines agency's perspective. Generics Biosimilars Initiat J 2012;1:89-91.

42. European Medicines Agency. Committee for medicinal products for human use (CHMP); 20-23 June 2009 - Plenary meeting monthly report. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2011/07/WC500108232.pdf

43. Jeong YH, Koh IS, Kang MK, et al. The impact of generic clopidogrel bisulfate on platelet inhibition in patients with coronary artery stents: results of the ACCEL-GENERIC Study. Korean J Intern Med 2010;25:154-61.

44. Oberhänsli M, Lehner C, Puricel S, et al. A randomized comparison of platelet reactivity in patients after treatment with various commercial clopidogrel preparations: the CLO-CLO trial. Archiv Cardiovasc Dis 2012;105:587-92.

45. Rao TR, Usha PR, Naidu MU, et al. Bioequivalence and tolerability study of two brands of clopidogrel tablets, using inhibition of platelet aggregation and pharmacodynamic measures. Curr Ther Res Clin Exp 2003;64:685-96.

46. Ashraf T, Ahmed M, Talpur MS, et al. Competency profile of locally manufactured clopidogrel Low-plat and foreign manufactured clopidogrel Plavix in patients of suspected ischemic heart disease. J Pak Med Assoc 2005;55:443-8.

47. Marcucci R, Paniccia R, Gori AM, et al. Bioequivalence in the real world is a complex challenge: the case of clopidogrel. J Am Coll Cardiol 2013;61:594-5.

48. Doll J, Zeitler E, Becker R. Generic clopidogrel: time to substitute? JAMA 2013;310:145-6.

49. Fabrizio L. Il punto di vista della SIFO. Giorn Ital Farmacoecon Farmacoutil 2013;1:49.

50. Cordella L, Realdon N, Schievenin F, et al. I medicinali equivalenti. Dialogo sui Farmaci 2011:1-15. Available from: http://www.dialogosuifarmaci.it/app/webroot/documents/generici%20DSF%2017-10-2011.pdf

51. Nota AIFA sul Plavix. Prot. STD4/191.P del 16.02.2011. Available from: http://www.uvef.it/extfiles/10429/attachment/FILE1312811854559-38.pdf

52. Gazzaniga A, Maroni A. Bioequivalenza, intercambiabilità e sostituibilità. Giorn Ital Farmacoecon Farmacoutil 2013;1:21-5.

53. Peters JR, Hixon DR, Conner DP, et al. Generic drugs - safe, effective, and affordable. Dermatol Ther 2009;22:229-40.

54. World Health Organization. WHO Pharmaceuticals

Newsletter 1998, No. 11/12. Excipients: review of adverse reactions: France. Revue Prescrire 1998;18:595. Available from: http://apps.who.int/medicinedocs/en/d/Js2265e/2.3.html

55. Kalász H, Antal I. Drug excipients. Curr Med Chem 2006;13:2535-63.

56. Maroni A, Gazzaniga A. Pharmaceutical formulations of nimesulide. In: K.D. Rainsford, ed. Nimesulide, actions and uses. Basel: Birkhäuser; 2005. pp 121-13.

57. Goole J, Lindley DJ, Roth W, et al. The effects of excipients on transporter mediated absorption. Int J Pharm 2010;393:17-31.

58. Royal Pharmaceutical Society. British National Formulary: No 31. London: Pharmaceutical Press; 1996.

59. Endrenyi L, Tothfalusi L. Do regulatory bioequivalence requirements adequately reflect the therapeutic equivalence of modified-release drug products? J Pharm Pharmaceut Sci 2010;13:107-13.

60. Smith JC, Tarocco G, Merazzi F, Salzmann U. Are generic formulations of carvedilol of inferior pharmaceutical quality compared with the branded formulation? Curr Med Res Opin 2006;22:709-20.

61. European Medicines Agency. European Medicines Agency recommends precautionary recall of batches of clopidogrel-containing medicines from Acino Pharma GmbH - Press release; 25 March 2010. EMA/179606/2010. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/03/WC500076546.pdf

62. Osservatorio Federconsumatori 2012. Indagine sulla conoscenza dei farmaci equivalenti. Available from: http://www.federconsumatorier.it/download/ricerca-farmaci_giugno-2012-presentazione-pdf

63. Marzo A, Barassi A, Porro E. Open questions on bioequivalence: the case of cholecalciferol. Ital J Med 2013;7:156-9.

64. Marzo A, Reiner V. Open questions on bioequivalence: the case of multiple peak phenomenon. J Pharm Pharmacol 2004;56:281-2.