Low-quality of some generic medicinal products represents a matter for growing concern

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Abstract

Aims. Generic medicinal products (GMPs) are low-priced copies of off-patent medicines that reduce healthcare costs and broaden access to healthcare. Thus, healthcare authorities, professionals and providers, recommend their use. In recent years, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved hundreds of GMPs based on specific bioequivalent trials. The question is whether the brand-name drugs and GMPs or the different GMPs similar in purity, efficacy and safety.

Methods and Results. We have reviewed the progressive increasing recalls and warning letters of cardiovascular GMPs issued recently by the FDA/EMA. Both Agencies found numerous irregularities in the purity, safety, effectiveness and current good manufacturing practices in some GMPs widely used in cardiovascular therapy. This evidence and the recent identification of nitrosamine impurities classified as probable human carcinogens in several angiotensin receptor blockers confirm that the presence of low-quality/substandard GMPs represents a serious public health problem with significant impact on national clinical and economic burden.

Conclusion. A global strategy that unifies the efforts of all the stakeholders, including drug manufacturers, healthcare providers, Governments, health professionals, patients and judicial systems are needed to protect the drug chain supply and ensure that only high-quality GMPs are available for use.

Key words: brand-name drugs, generic medicinal products, bioequivalence, drug quality, inspection, regulation

Introduction

The rapid growth of the world's population, the remarkable improvement in life expectancy, the progressive increase of the population aged 65 and older with pluripathology and polypharmacy leading to a greater healthcare utilization, the increasing health care costs, and the recent economic crisis affecting many Western countries, put an enormous pressure on both public and private healthcare systems. Additionally, the progressive increase in prescription drugs and the growth of pharmaceutical expenditures due to new high-cost innovative medicines are exerting strong financial pressure and raise serious concerns about the financial sustainability of healthcare systems. Therefore, over the past 30 years, healthcare authorities, professionals, providers, and policymakers have promoted the therapeutic substitution of brand-name drugs (BDs) by generic medicinal products (GMPs), i.e. low-priced copies of a BD counterpart after the patent on original product expires, and restricts access to BDs as a strategy to reduce rapidly healthcare costs in most countries worldwide[1-4]. Therapeutic substitution. i.e. the interchange of a less costly drugs in place of another treatments, is based on the premise that GMPs have the same efficacy and safety than BDs[5]. GMPs availability, but not their use, may provide substantial cost savings for national healthcare systems, patients and third-party payers, improve access to drugs for more patients with chronic conditions and release resources to pay for newer innovative treatments[1-4,6,7] (Table 1). However, in many healthcare systems, the availability of a GMP sets the reference price to which that drug is reimbursed. Therefore, the use of a BD or of a GMP does not affect the budget impact of the given drug as the healthcare system will reimburse only for the reference price. Additionally, in some countries (i.e. Spain) the price of BDs and GMPs is the same; so, there is no financial advantage.

A consolidated generic drug industry producing effective and safe drugs coupled with a sufficient number of manufacturers to stimulate competitive pricing and avoid an increase in GMP costs are essential to keep a sustainable healthcare system[7]. In 2017, the global generic drug market was around US$ 244.5 billion, which represents ~17% of the value of the global pharmaceuticals market, growing at a compound annual growth rate of around 8% during 2010-2017[6,8]. In the United States, GMPs represent ~90% of total ($3.9 billion) prescriptions annually[6,8], while in Europe they represent 50–70% of prescriptions[9]. Furthermore, the Association for Accessible Medicines (AAM) estimated that the use of GMPs saved approximately $1.6 trillion between 2004 and 2013 ($253 billion in 2016)[8] and Medicines for Europe that the European healthcare systems saved €100 billion in 2014[9].

In recent years, the Food and Drug Administration (FDA) approved an increasing number of GMPs, from 813 in 2016 to over 1000 new GMPs in 2017 and 2018[10]. Because of this progressive increase in GMPs we need to answer two important questions: are the BDs and GMPs similar in purity, efficacy and safety? and, are the different GMPs of a given BD similar in purity, efficacy and safety?.

Interestingly, very recently, the number of drug recalls (i.e., voluntary actions taken by a company at any time to remove a defective drug product from the market), warning letters issued by the FDA and European Medicines Agency (EMA) related to violations in current good manufacturing practices (CGMP) and substandard (defined as pharmaceutical products that do not meet their quality standards and specifications) or contaminated GMPs have progressively increased. These findings raised serious concerns in patients, physicians and policymakers. In this article, we analyze the similarities and differences between BDs and GMPs, where medicines came from, the reasons for the recent increase in low-quality/substandard or contaminated GMPs and, finally, how we can fight against these GMPs. Please, note that we refer exclusively to "low-quality/substandard or contaminated GMPs", but not to the GMPs in general. Indeed, we would like to emphasize that high-quality GMPs play an important role in the daily treatment of our patients and contribute to the sustainability of the healthcare system.

Similarities and differences brand name and generic medicinal products

1. Similarities. GMPs are considered pharmaceutical equivalents of BDs if they contain identical amounts of the same active ingredient(s), same pharmaceutical form, same route of administration and if they meet the same standards for strength, purity, quality, and identity[6,7,11,12]. Market authorisation of a GMP requires the demonstration of bioequivalence (BE), defined as the absence of a significant difference in the rate and extent to which the active ingredient or moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when they are administered at the same molar dose under similar conditions in an appropriately designed study[11,12]. The selected pharmacokinetic parameters used to establish BE include: the area under the plasma concentration–time curve (AUC), a theoretical measure of the total exposure of drug to the body from administration till all the drug is eliminated, and the maximum plasma concentration (C_{max}) and the time to reach the C_{max} (T_{max}) which are influenced by the rate of absorption. Bioequivalence is established when, for both AUC and C_{max}, the 90% confidence intervals for the ratio of geometric means for test and reference formulations lie within the range of 80% and 125%[11,12]. In practice, this means that the two drugs have the same therapeutic effect (within statistical limits), by delivering the same amount of drug to the body over the same period of time. The 90% confidence intervals for the AUC ratio is tightened (90-111.11%) for narrow therapeutic index drugs. The similarities and differences between between GMPs and BDs are summarized in Table 2.

However, it is possible that two GMPs that are at the far opposite range of BE limits (-15% for drug D and +20% for drug E) can be both bioequivalent with respect to the BD, but not bioequivalent to each

other, which may result in either over- or under-dosing when a patient is switched between different GMPs of the same BD (Figure 1). Furthermore, in some occasions, a GMP can become the reference standard for the approval of another GMP that in turn can become the reference for another GMP and so on. If the approved GMPs are in the lower range of BE then the last GMP approved may have significantly less efficacy due a process known as *bio-creep*, and the different GMPs are not bioequivalent (Figure 2). This phenomenon of comparator degeneration indicates that a GMP should never be used as comparator as long as a BD is available.

These findings are of clinical interest, because with the proliferation of GMPs, patients are frequently switched from different versions of the same GMP without notification to the patient or to the prescriber, just because different pharmacies have different GMPs or the same pharmacy changes from generic suppliers looking for the cheapest GMP available. This practice is based on the assumption that the products being substituted are bioequivalent. However, due to the lack of comparative studies of BE between GMPs of the same BD and because BE studies are typically not registered or published (see below), physicians, pharmacists and patients cannot make the best choice.

Because GMPs are used by millions of patients, their evaluation must be highly transparent, with registration of the trial protocols and publication of results of registered trials[13]. Unfortunately, reports of BE trials assessing GMPs are not available on FDA or EMA websites. Important information such as funding source, country where the trial was performed, reference drug used (the BD or another GMP) and details about the methodology are frequently missing[13]. A publication bias may also affect BE trials comparing GMPs vs BDs because it is very unlikely that only 10% of trials failed to demonstrate BE. Flacco et al[14] analyzed the randomized trials comparing the safety or efficacy of BDs vs GMPs registered in ClinicalTrials.gov or other registries from January 1, 2000, through July 31, 2015. During this period of time more than 2,900 generic drugs were approved by the FDA. However, they only identified 207 registered protocols reporting on 186 completed trials. Four years after trial completion, results were available for 64 of 138 trials (46.4%), with substantial differences by sponsor and almost all trials (95.7%) reported favourable results of GMPs. Thus, despite their wide use, there is an associated unsatisfactory publication rate and publications are at high risk of bias in favour of GMPs and regulatory agencies may need to apply stronger pressure on generic manufacturers to register and publish results of clinical trials comparing GMPs vs BDs.

Furthermore, a recent study of events reported to the FDA Adverse Event Reporting System (FAERS) from the 2004 to 2015 showed that even when GMPs accounted for the majority of dispensed prescriptions, BDs accounted for a high number of reports even after generic drug market entry[15]. Similarly, the Institute for Safe Medication Practices (ISMP) confirmed that BDs accounted

for <5% of dispensed prescriptions of the most widely used drugs, but BD manufacturers submitted around 68% of all serious adverse reports[16] and manufacturers of GMPs heavily underreport deaths caused by clopidogrel to the FDA[17]. Thus, the final conclusion is that the safety profile of GMPs is not properly reported and post-marketing surveillance of GMPs should be improved.

2. Differences. Although FDA and EMA require that GMPs contain the same active ingredient(s) as the BDs, GMPs differ from BDs and from other GMPs of the same BD in pill colour, shape, taste, specific manufacturing process and in inactive ingredients, known as excipients[18]. Pharmaceutical excipients include binders, diluents, dispersants, disintegrants, lubricants, coaters, sweeteners, flavourings, dyes and preservatives. However, even when the type and quality of excipients are crucial to drug delivery within the body they are less likely to come under scrutiny. This is an important point, because[18-21]: a) generic manufacturers may not even know what inactive ingredients are in the BD or in other GMPs. b) There may be important differences in the excipients in different formulations of the same GMP. c) Manufacturers can change the suppliers of APIs and excipients without being required to undertake new BE studies. Variations on the type and quality of excipients and manufacturing procedures can impact drug release and can explain why BE curves of a given GMP might vary over time as well as some differences in efficacy between batches of the same GMP and between different GMPs of the same BD. d) Different excipients can be related with the loss of response and may lead to unintended appearance of adverse effects during treatment with GMPs.

The ACCF/AHA 2011 Health Policy Statement on Therapeutic Interchange and Substitution recognized that some additives traditionally thought to be inert, such as alcohol sugars, bisulfites, cyclodextrans, and polysorbate-80, may alter a drug's dissolution, thereby impacting its bioavailability[22,23]. Some excipients can influence gastrointestinal transit time and drug absorption (sorbitol reduces the C_{max} of metoprolol and ranitidine[24]), generic formulations of propafenone or verapamil containing a lactose-based excipient can lead to gastrointestinal disturbances[25], surfactants may affect transport proteins and drug absorption, and the presence of croscarmellose sodium can explain allergies to generic furosemide, while tartrazine and bisulfites can cause severe allergies or asthma[19,26].

The rate of dissolution of a product within the gastrointestinal tract can influence the rate of drug absorption. Thus, under certain circumstances, *in vitro* testing of drug-specific limits for dissolution times as defined in pharmacopoeias are used to document product bioavailability and BE, manufacturing variations that might influence bioavailability, check batch-to-batch consistency and characterize drug release mechanisms and formulation bioequivalence[27,28]. There are examples of important variations in dissolution times between BDs and their supposedly bioequivalent GMPs which clearly question the inter-changeability between the branded and its generic counterpart or

even among GMPs[29-31]. Additionally, small changes in excipients can lead to differences in particle size or modify the shelf-life and hence affect drug disposition, efficacy and safety[19,].

Even if the same quantity of API is contained in each preparation it is difficult to establish proper dissolution test conditions/parameters and BE for modified-release formulations because of prolonged gastrointestinal residence of the dosage form and variabilities in physiological conditions of the gastrointestinal tract. Thus, it is generally not recommended to substitute modified-release formulations of some β-blockers, calcium channel blockers and theophylline with generic versions[21,27,32]. The difficulties arise because when a BD becomes a GMP, the patent of the time-release mechanism is not available and the generic company has to develop its own release mechanism[20]. This explains the marked variations in the time-release mechanisms according to different manufacturers.

There may be also differences derived from changes in origin and quality of raw materials; alternative chemical routes to synthesize the GMP (to avoid patent infringement); conditions in which the chemical reactions take place; reagents, solvents and purification phases; and presence of impurities different from original. Both EMA and FDA require all ingredient suppliers to register if their products are used in drugs made or sold in the EU/US. However, regulations apply only to manufacturing, not to pre-production steps such as collecting and extracting raw materials, an important aspect for unfractionated heparin.

Where do my medicines come from?

When patients pick up the prescriptions from the pharmacy or open their medical cabinet they trust that they are effective and safe, but they do not know where they came from. Even when medicines come from anywhere around the world, nearly 80% of the APIs (active pharmaceutical ingredients) and 40% of finished medications are imported from overseas, mainly China and India[33]. In these two countries is where almost 80% of registered ingredient manufacturers are located.

The pharmaceutical supply chain is a complex, fragmented and interconnected global network of raw materials suppliers, chemical producers, brokers, manufacturers, packagers/re-packagers, suppliers and distributors[34]. The active ingredient of the GMP might be synthesized in China, the excipients in India, some raw materials came from another country and they may be manufactured into active ingredients in another one. Then, they can be processed and repackaged in a country of the European Union (EU) and, finally, sent to different European countries for final production and distribution to the local pharmacy. Interestingly, quite often a few manufacturers supply APIs to many companies that use them to make pills or sometimes they sell the pills to other companies for repackaging. Moreover, many GMP suppliers contract manufacturers that prepare the products that

they simply label with their brand. Thus, it is clear that there are many weak points along this pharmaceutical chain and every transaction is an opportunity for substandard products to infiltrate the market[34].

All medicaments must comply with the so-called CGMP. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories[35]. Drug manufacturers are responsible for: a) ensuring the purity and quality of the APIs and excipients of all medicines they import or market according with the standards and specifications of the European and U.S. Pharmacopoeia at release and throughout the product shelf-life required by the territory of use; b) how medicines are consistently stored, transported and handled under suitable conditions; and c) developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If new or higher levels of impurities are detected, they should report them and take a rapid action to ensure the product is safe for patients. However, current labelling of GMPs do not require the identification of the manufacturer responsible for the CGMP or their country of origin and suppliers can simply mention the national distributor on the label.

The recent increase in adulterated or contaminated generic medicinal products

GMPs must be identical in purity, efficacy and safety to BDs. Substandard or contaminated medications can reach the market as a result of a variety factors, including unintentional production mistakes (or, possibly, negligence), inadequate quality-control processes during manufacture that cause contamination or lack of sterility, incorrect storage or inappropriate packaging design and/or poor management oversight, or deliberately fraudulent practices[5,35]. Ineffective quality-control measures, either by the generic manufacturer or National Medicines Regulatory Authorities, allow for such faults to remain undetected.

In recent years, EMA and FDA found increasing evidence of numerous irregularities in the purity, safety and effectiveness of CGMP of GMPs (Tables 3 and 4) and the number of drug recalls and of warning letters issued by the FDA's Office of Manufacturing and Product Quality to companies that have failed to comply with the CGMP increased between 2015 and 2018 from 42 to 127 (for a review see 36). Furthermore, the number of banned drugs both by FDA and the EMA significantly increased due to the presence of impurities and contaminations, including among others small glass particles in atorvastatin tablets, degradation products in streptokinase (Figure 3) and clopidogrel or the presence of fungal encephalitis with heparins[29-31,37-43] (for a review, see Tables 3 and 4). There are also examples of differences in CGMP violations of manufacturing practices and falsification of seminal information on drug applications (chromatography tests, electrocardiograms, BE studies) (Table 4).

Furthermore, FDA and EMA have also banned hundred of drugs coming from overseas[6], but probably the most relevant example of contamination of GMPs arose in July 2018. From that date, several pharmaceutical companies have voluntary recalled many lots of several angiotensin receptor blockers-ARBs (irbesartan, losartan and valsartan, alone or in combination with amlodipine and/or hydrochlorothiazide), due to unacceptable amounts of three nitrosamine impurities [nitrosodiethylamine (NDEA), N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA)] which are potentially carcinogens, in the APIs manufactured by Zhejiang Huahai/Tianyu Pharmaceutical Co. Ltd. (China) and Hetero Labs Ltd (India)[44] (Table 3). As a result, one third of FDA recalls involved ARBs-containing products, and the recalls have affected one sixth of U.S. ARB manufacturers[44]. Consequently, medical agencies across Europe and FDA withdrew all contaminated products from the market since July 2018. A change in manufacturing tetrazoles (a 5-member ring of four nitrogen atoms and one carbon atom present in irbesartan, losartan and valsartan) patented by the Chinese pharmaceutical company Zhejiang Huahai resulted in the inclusion of these impurities[45,46]. EMA identified the reaction of dimethylamine and sodium nitrite under acidic conditions during the manufacturing process as a potential source of NDMA[47]. These findings make us to suspect that other ARBs containing a tetrazole ring (candesartan, olmesartan) might also be contaminated. Of note, more than 61 million prescriptions were written for valsartan, irbesartan, or losartan in the U.S. in 2016 and FDA and EMA officials believe that patients have been ingesting contaminated ARBs for approximately 4 years[44].

These recalls create serious concerns and anxiety in patients, clinicians, and pharmacies. They also increase the mistrust between patients and providers and question the ability of the healthcare systems to promptly respond to patients' concerns and ensure the quality of the medications doctors prescribe to patients[44]. Some clinicians switched patients from one ARB that was initially recalled (valsartan) to another ARB that was recalled later (irbesartan or losartan), which distrusts the confidence of the patients in their clinicians, health care system and the drug supply chain[44,45]. Interestingly, the recall of valsartan included almost all lots of valsartan on the market, including the GMP marketed by Sandoz (the generic pharmaceuticals division of Novartis), while the original valsartan from Novartis was unaffected by the recall, possibly because of the different origin of the API. Furthermore, hypertensive patients hear about a recall of a "hypertension drug", but they did not know the specific GMP and manufacturer involved and, more important, it was not mentioned that ARBs are also first choice drugs in the treatment of patients with heart failure, chronic kidney disease or diabetes mellitus who may ignore the recall. Fortunately, because not all products containing irbesartan, losartan and valsartan contained NDMA, NDEA or NMBA impurities, pharmacists could refill the stores with uncontaminated medications, and doctors prescribe an alternative drug that

treats the same condition. Of note, some unaffected manufacturers have taken advantage of the situation to increase the prices of their ARBs 2-5 times.

The magnitude of the problem is much greater if we analyze the number of GMPs banned by the European Medicines Agency in the last 3 years because some of them are considered critical in our daily clinical practice (Table 5). Note that many drugs that receive a class I recommendation in the ESC guidelines for the treatment of arterial hypertension, heart failure, diabetes mellitus, atherothrombotic diseases, chronic kidney disease or pulmonary arterial hypertension were involved. Furthermore, many widely used antidepressants, antibiotics (β-lactam antibiotics, macrolides), azole antifungals, corticosteroids, H1-antihistaminics, or vasodilators were also banned from exporting to the EU or U.S. Thus, the problem of substandard or low-quality GMPs is a matter for growing concern.

We need to fight against low-quality generic medicinal products

Frequently problems related to low-quality or contaminated GMPs are detected too late because of infrequent inspections of generic pharmaceutical companies or manufacturing site(s) or after substandard products have already caused adverse effects in patients. Thus, better controls on the wholesale market could improve the security of the distribution chain and protect patients. Some suggestions to fight against low-quality/contaminated GMPs and improve the confidence on GMPs are summarized in Table 6.

Regulatory authorities (FDA and EMA) continuously monitor drug products and perform periodic inspections of the manufacturing plants around the world (but mainly in China and India) to guarantee that, at all levels of the global supply chain, the medicaments we take are effective, safe, and of high quality (i.e., they are not contaminated, counterfeited, corrupted or mislabelled) before and after they are marketed. EMA/FDA conduct unannounced inspections of domestic drug manufacturing establishments, on average, every two years, whereas foreign drug facilities are inspected only every several extra years. Furthermore, in India and China inspections “must be conducted” with the cooperation and facilitation of national regulators and, sometimes, the approval of those inspected, which clearly limits their value[48]. The good news is that FDA/EMA have increased the annual number of foreign drug establishments subject to inspection; the bad news is that both agencies currently lack information of more than 30% of the foreign drug facilities (64% in 2010). Many foreign drug establishments have never been inspected and it is uncertain whether the quality can be significantly compromised. Thus, at the present time there is room for improvement in the surveillance of foreign facilities to ensure that patients have access to safe, high-quality, and affordable GMPs.

Even when surprise plant inspections can not prevent all problems related with non-bioequivalent and even substandard products, recent episodes of contaminated GMPs and the increased number of drug recalls strongly suggest that it is necessary to increase the frequency of inspections at all levels of the pharmaceutical supply chain and the frequency and extent of pharmacovigilance, especially market surveillance, monitoring the safety of a GMP after it has been released on the market throughout its life span[34]. However, both FDA and EMA do not have the resources needed to perform independent clinical studies as they are under staffed and under funded and lack the regulatory authority to require the generic pharmaceutical companies to conduct such studies. Both agencies are also unable to conduct enough market surveillance and/or perform independent clinical studies to investigate some reports claiming that some GMPs do not act in the same manner as BDs. Because of limited resources, the large number of foreign drug facilities, the increasing number of products entering the EU/U.S. from overseas, and the lack of a regulatory authority, EMA and FDA sometimes use a risk-based selection model to select domestic and foreign establishments for inspection, given priority to those making drugs which, if defective, pose the greatest public health risk. Additionally, FDA and EMA "encourage the generic industry" to investigate whether, and under what circumstances, problems occur.

Therefore, FDA and EMA need a stable funding budget to perform inspections overseas and to monitor the thousands of medicines and their ingredients coming from domestic plants and imported from overseas. Interestingly, the 2012 Generic Drug User Fee Act authorizes FDA to collect user fees from manufacturers of GMPs, including those who supply active ingredients for generics, for conducting more foreign inspections to ensure patients have access to high-quality GMPs. Unfortunately, the EU has not provided an equivalent financial support for the EMA.

The European Union (EU) has signed mutual recognition agreements with third-country authorities that aim to facilitate market access and encourage greater international harmonisation of compliance standards while protecting consumer safety. Since 2014, FDA and EMA collaborate in the way they each inspect drug manufacturers and assess the risk and benefits of mutual recognition of drug inspections. The mutual recognition agreement between agencies allows the EU (with all Member States recognised as a single entity) and the US to harmonise requirements regarding quality, safety and efficacy of medicinal products, to rely upon information from drug inspections conducted within each other's borders and to exchange confidential information on inspection reports. This cooperation avoid current duplication of inspections, safe costs and enables reallocation of resources towards inspection of drug manufacturing facilities with potentially higher public health risks[49].

Finally, to fight against low quality GMPs it is not enough to ban imports and more drastic measures including law enforcement, empowering states to prevent and respond to drug quality problems are

needed. The Council of Europe has long been concerned about the absence of harmonised international legislation, the mismatch between the sanctions and the harm caused to patients, and the involvement of criminal organisations operating across borders. The Medicrime Convention is the first European criminal law instrument to force Member States to criminalise the adulteration or contamination of GMPs and similar offences posing serious threats to public health[50].

Conclusions

In recent years, the number of drug recalls and warning letters issued by the FDA/EMA related to violations in CGMPs and low-quality, substandard or contaminated GMPs have progressively increased. Low-quality GMPs represent an increasing public health problem and even when their long-term effects on public health are hard to quantify, they clearly have an enormous negative economic impact not only on patients as they will lose confidence in the medicaments in general, but also on healthcare providers and national health systems. Because global drug supply chains have become more and more complicated, crossing continents, we need a comprehensive global strategy that unifies the efforts of all the stakeholders including drug manufacturers, care providers, Governments, health professionals, patients and judicial systems. They must all act together to protect the drug chain supply and ensure that only high-quality GMPs are available for use. An increase in the frequency of inspections of domestic and foreign drug establishments at all levels of the pharmaceutical supply chain and of pharmacovigilance, especially market surveillance, and in the funding of FDA and EMA, the Mutual Recognition Agreements between Agencies and law enforcement to criminalise the adulteration or contamination of GMPs and similar offences posing serious threats to public health, are needed to guarantee the purity, efficacy and safety of GMPs.

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Figure legends

Figure 1. Two generic medicinal products (GMPs) that are bioequivalent to the BD may not be bioequivalent to each other. Illustration of six hypothetical GMPs with their 90% confidence limits for their area under the curve (AUC). Generic medicinal products A, D, E and F meet the criteria and are bioequivalent to the band-name drug (BD), while products B and C are not bioequivalent because the AUC 90% CI falls outside the bioequivalence limits (80-125%). GMPs D and E would also be approved because they are bioequivalent to the BD, but are near the limits of the 80%–125% range and are statistically dissimilar to each other, i.e. they are not bioequivalent. Generic product F, fulfil the criteria of bioequivalence, but the effects of this GMP are more variable than those of the other bioequivalent formulations.

Figure 2. If the reference drug is not the brand-name drug but a generic medicinal product, a bio-creep phenomenon leading to a significant loss of biavailabity (BA) compared to the brand-name drug could occur. BA: bioavailability. GMP: generic medicinal product.

Figure 3. Streptokinase activity of sixteen streptokinase preparations (three of which were recombinant) available on Brazil, India, Jordan, China, Pakistan or Europe, according to the origin (distributors and manufacturers) of the samples. There are wide variations between claimed and measured streptokinase activity, purity and composition of the tested products and only three fulfilled the minimum requirements of the European Pharmacopoeia. Modified from Hermentin et al[37].

Table 1 . Main advantages of prescribing generic medicinal products

1. The main difference is that GMPs are generally cheaper than BDs. As a consequence, GMPs:

- Reduce total national healthcare costs
- Contribute to the sustainability of the healthcare system
- Release resources to pay for newer innovative treatments
- Provide substantial cost savings for patients and third-party payers
- Improve health outcomes by facilitating better access to drugs for more patients with chronic conditions
- Increase patient compliance to their medication regimens

BDs: brand-name drugs. GMPs: generic medicinal products.

Table 2. Comparison between brand name and generic medicinal products

Similarities	Differences
They must have the same: • Active substance(s) • Amount of active substance (strength) • Pharmaceutical form • Route of administration • Indications • Batch requirements for identity, strength, purity and quality • Strict standards of CGMP regulations	They can have different: • Sizes • Colour • Shape • Inactive components • Packaging
They are bioequivalent, i.e. deliver similar amounts of the active ingredient to the bloodstream	The only consistent difference is that GMPs are less expensive than BDs
GMPs are approved based on BE studies • Safety and efficacy testing is not required	BDs are approved after phase I-III clinical trials confirmed their efficacy and safety as compared with the standard therapy
BE studies are performed in: • Homogeneous populations • Young (male) healthy volunteers • Small sample sizes • Without comorbidities • Short-term administration • "Clean" of other drugs	Clinical trials are performed in: • Heterogeneous populations • Target patients • Large sample sizes • With comorbidities • Long-term administration • Patients receiving other drugs

BDs: brand name drugs. BE: bioequivalence. CGMP: current good manufacturing practice. GMPs: generic medicinal products.

Table 3. Changes in drug content or stability, problems in solubility, presence of impurities and/or contaminations in cardiovascular generic medicinal products

Date, Agency	Comments
Gomez et al., 2004[29]	In an analysis of 18 copies of clopidogrel over 60% of the GMPs contained higher amounts of impurities, lower content of clopidogrel and different dissolution profiles. After storage for 3 months at 40°C and 75% humidity, the differences were more pronounced
Hermentin et al., 2005[37] (Europe, Asia and South America)	Wide variations in the activity, purity, and composition 16 streptokinase preparations from different manufacturers and distributors. Thirteen out of 16 products exhibited 20.8 to 86.6% of the activity stated in the label (declared value 90-111%)
Smith et al., 2006[30] (Europe and US)	An analysis of carvedilol generic medicinal products from 20 manufacturers in 19 countries found that at least 17/35 (48.6%) GMPs failed the specifications of the EP due to: incorrect drug content, excess impurities (> 0.3%), incorrect tablet hardness and inadequate dissolution
Blossom et al., 2008[38] (US)	Serious adverse effects (hypotension, angioedema, shortness of breath) and some deaths due to the use of heparin imported from China contaminated with a semi-synthetic over-sulphated chondroitin sulphate were identified in 13 US States. Baxter Healthcare Co. voluntarily recalled heparin lots
Angelli and Trezza, 2009[31]	In a comparison of 22 marketed ramipril generic medicinal products, only 24% were equivalent in quality, stability and dissolution profiles to that of the reference product. Total levels of impurities were above reference ramipril specifications in 32% of GMPs at baseline, increasinng to 68% at 3 months
Blossom et al., 2009[39] (US)	Multistate outbreak of 162 *Serratia marcescens* bloodstream infections associated with contaminated prefilled heparin and isotonic sodium chloride solution syringes were identified 9 US States. FDA revealed poor compliance with the FDA's GMPs and quality system regulations
Mastoraki et al., 2008 [40] (Greece)	Higher incidence of postoperative infections in adult patients undergoing coronary artery bypass grafting surgery treated with the generic cefuroxime instead of original cefuroxime as antimicrobial prophylaxis
12/06/2010, FDA Zoler et al., 2010[41] (India and Europe)	Several generic medicinal products containing clopidogrel marketed in India and Europe contained significant levels of methyl chloride, a known toxin and mutagen.
09/01/2011, FDA	Sun Pharmaceutical Industries deleted more than 5,300 which failed chromatography test results
02/03/2012, Choudary, 2012[42] (Lahore, Pakistan)	107 deaths and serious adverse reactions in more than 450 patients due to contamination of isosorbide mononitrate with pyrimethamine due to a manufacturing error
10/22/2012, FDA Kainer et al., 2012[43]	Recall injectable methylprednisolone acetate compounded at New England Compounding Pharmacy's facility in Framingham (Massachusetts) and contaminated with enviromental molds (*Exserohilum rostratum*) after an outbreak of fungal infections (meningitis included) caused 64 deaths (8%)
12/12/2012, FDA	Identified bacterial and/or fungal contamination in unopened vials of betamethasone and triamcinolone solutions
05/13/2013, FDA	Generic drug manufacturer Ranbaxy Laboratories (India) pleaded guilty in US to seven federal criminal counts of selling adulterated GMPs with intent to defraud. The company agrees to pay a total of $500 million to

	resolve false claims allegations, CGMP violations and false statements to the FDA
November/2013, FDA	The FDA's computer forensics experts found 5,301 additional deleted results from chromatography tests at Sun Pharmaceutical Industries Ltd. (India)
03/08/2014, FDA	Ranbaxy Pharmaceuticals, recalled 480,000 bottles of the generic medicament atorvastatin, after tiny shards of glass were found inside pills
05/30/2014, FDA	Zydus Cadila recall 10,200 bottles of promethazine due to the presence of atenolol
06/23/2014, FDA	Wockhardt and Dr. Reddy's Laboratories announced recalls of more than 100,000 bottles because their products were not dissolving properly
9/30/2015	38 facilities in China banned from exporting to U.S.
12/23/2015, FDA	Significant violations of CGMP in two Cadila Healthcare Limited pharmaceutical manufacturing facilities (India)
05/05/2018, EMA	Valsartan contaminated with NMDS, a probable human carcinogen, found in Zheijiang Huadai Pharmaceuticals (China)
05/07/2018, EMA	Detect the impurity NDMA in medicines containing valsartan manufactured by Zhejiang Huahai Pharmaceuticals (China). EMA recalled approximately 2300 batches of valsartan products
07/13/2018 up to April 2019, FDA	Voluntary recalls of several re-packagers of several valsartan-containing products (updated April 11, 2019) manufactured by Hetero Labs Limited (India) and/or Zhejiang Huahai Pharmaceuticals (China) due to the presence of NDMA • Valsartan: American Health Packaging (Aurobindo); A-S Medication Solutions LLC (Teva/Actavis & Prinston/Solco); Aurobindo Pharma USA, Inc.; Aurobindo Pharma USA, Inc. (Acetris); AvKARE, Inc. (Hetero/Camber); Bryant Ranch Prepack Inc. (Teva/Actavis); H J Harkins Company Inc. dba Pharma Pac (Prinston/Solco); Hetero Labs, Inc.; Major Pharmaceuticals; Mylan Pharmaceuticals, Inc.; Northwind Pharmaceuticals (Teva/Actavis); RemedyRepack, Inc. (Hetero/Camber); Rising Pharmaceuticals Inc; Teva Pharmaceuticals USA Inc.; Torrent Pharmaceuticals Ltd. • Valsartan/HCTZ: A-S Medication Solutions LLC (Teva/Actavis & Prinston/Solco); AvKARE, Inc. (Teva/Actavis); Mylan Pharmaceuticals, Inc.; Northwind Pharmaceuticals (Teva/Actavis); NuCare Pharmaceuticals Inc. (Prinston/Solco); RemedyRepack Inc. (Prinston/Solco); Solco Healthcare LLC. (Prinston); Teva Pharmaceuticals USA Inc.; Torrent Pharmaceuticals Ltd. • Amlodipine/valsartan: Aurobindo Pharma USA, Inc.; Mylan Pharmaceuticals, Inc.; Teva Pharmaceuticals USA Inc • Amlodipine/valsartan/HCTZ: RemedyRepack, Inc. (Torrent); Teva Pharmaceuticals USA Inc.; Torrent Pharmaceuticals Ltd
01/10/2018 up to April 2019, FDA	Voluntary recall of irbesartan-containing products due to the presence of NDEA • Irbesartan: Prinston Pharmaceutical Inc., dba Solco Healthcare LLC • Irbesartan/HCTZ: Prinston Pharmaceutical Inc., dba Solco Healthcare LLC Aurobindo Pharma USA, Inc.; ScieGen Pharmaceuticals (labeled as GSMS Incorporated or Westminster Pharmaceuticals)
	Levels of NDEA in losartan-containing products due to the presence of NDEA • Losartan: AvKare (TorrentTorrent Pharmaceuticals Ltd); Camber

	Pharmaceuticals, Inc.; H J Harkins Company Inc dba Pharma Pac (Camber); Legacy Pharmaceutical Packaging, LLC (Hetero/Camber); Legacy Pharmaceutical Packaging, LLC (Hetero/Camber); Preferred Pharmaceuticals, Inc. (Torrent); Torrent Pharmaceuticals Limited • Losartan/HCTZ: AvKare (TorrentTorrent Pharmaceuticals Ltd); Macleods Pharmaceuticals; Sandoz Inc.; Torrent Pharmaceuticals Ltd
	Voluntary recall of valsartan-containing products due to the presence of NDEA • Valsartan: Acetris Health LLC; Aurobindo Pharma USA, Inc.; Mylan Pharmaceuticals, Inc. • Valsartan/amlodipine: Acetris Health LLC; Aurobindo Pharma USA, Inc.; Mylan Pharmaceuticals, Inc.; Teva Pharmaceuticals USA Inc. • Valsartan/HCTZ: Aurobindo Pharma USA, Inc.; Mylan Pharmaceuticals, Inc • Valsartan/amlodipine//HCTZ: Mylan Pharmaceuticals, Inc.; Teva Pharmaceuticals USA Inc.
03/01/2019, up to April 2019, FDA	Voluntary recall of losartan-containing products made by Hetero Labs (India) due to the presence of NMBA: • Losartan: AvKare (Torrent); Camber Pharmaceuticals Inc.; Torrent Pharmaceuticals Ltd; H J Harkins Company Inc dba Pharma Pac (Camber); Legacy Pharmaceutical Packaging, LLC (Hetero/Camber and Torrent); Preferred Pharmaceuticals, Inc. (Torrent); Torrent Pharmaceuticals Ltd. • Losartan/HCTZ: AvKare (Torrent); Macleods Pharmaceutical Ltd.; Sandoz Inc. ; Torrent Pharmaceuticals Ltd.
	Voluntary recall of valsartan-containing products made by Hetero Labs (India) due to the presence of NMBA: • Aurobindo Pharma USA, Inc.

ARBs: angiotensin II receptor blockers. BE: bioequivalence. CGMP: current good manufacturing practice, EMA European Medicines Agency. EP: European Pharcopoeia. FDA: Food and Drug Administration. GMPs: generic medicinal products. HCTZ: hydrochlorothiazide. NDEA: N-nitrosodiethylamine. NDMA: N-nitrosodimethylamine. NMDS: N-dinitrosodimethylamine.

Table 4. Recent banned imports of generic medicinal products raised by the EMA and/or FDA

Date, Agency	Comments
03/25/2010, EMA	Recall all batches of eight centrally-authorised generic medicinal products containing clopidogrel manufactured by Glochem Industries Ltd (India). The marketing authorisation holder of all these medicines was Acino Pharma GmbH
01/25/2012, FDA	Department of Justice files consent decree of permanent injunction against Ranbaxy; this company continued to violate CGMP regulations and falsify information on drug applications
08/22/2012, FDA	Withdraw approval of 27 abbreviated new drug applications (ANDAs) held by Ranbaxy Laboratories Ltd. • Amoxicillin, cefaclor, cefprozil, etodolac, flucomazole, ganciclovir, glimepidide, metformin, pravastatin, ramipril, terazosin
06/23/2014, FDA	Recall of more than 13,000 bottles of metoprolol succinate extended release tablets manufactured by Dr. Reddy's Laboratories
08/26/2013,FDA	Zydus Pharmaceuticals USA has recalled one lot of 2 mg warfarin tablets due to an increased pharmacological effect of the drug
01/11/2014, FDA	FDA inspections identified significant CGMP violations and prohibited Ranbaxy's Toansa, India facility from producing and distributing GMPs for the U.S. market, including (among others): • Amlodipine/valsartan, atenolol, atorvastatin, benzepril, clindamycin, felodipine, fluoxetine, furosemide, lisinopril, metoprolol, minocycline, onsasetron, pioglitazone
04/02/2014, FDA	FDA has banned generic drugmaker Apotex (India) from importing GMPs made in Bangalore after discovering CGMP violations
09/19//2014, FDA	US bans importation of all but one product from Apotex (India) after its inspectors found that staff had manipulated data, retested samples until they got favourable results and destroyed records.
09/25/2014, EMA	Recommends to suspend hundreds of GMPs due to manipulations of electrocardiograms during the BE studies performed over a period of at least 5 years in GVK Biosciences (Hyderabad, India)
2014, FDA	At least twelve pharmaceutical companies with facilities in India were banned from shipping GMPs to the U.S. due to violations of CGMP
23/01/2015, EMA	Recommends the suspension in 30 European countries of 700 GMPs manufactured by GVK Biosciences (India) due to manipulations of the electrocardiograms during BE studies over a period of at least 5 years. Some of these medicinal products may be considered critical by the individual EU Member States. • Aciclovir, alendronic acid, amlodipine, atorvastatin, bosentan, candesartan, cefpodoxime, ciprofloxacin, clindamycin, clonazepam, clobazam, clopidogrel, desloratadine, desmopressin, dipyridamole, donezepil, ebastine, eletriptan, entacapone, esomeprazol, escitalopram, fexofenadine, fluconazole, hydrocortisone, ibuprofen, irbesartan, irbesartan/HCTZ, levetirazetam, levodopa/carbidopa/entacapone, metformine, metoclopramide, nebivolol, pantoprazole, phenoxymethylpenicillin, pioglitazione, quetiapine, repaglinide, rizatriptan, ropinirole, tacrolimus, telmisartan, telmisartan/HCTZ, thiamine, tramadol, tramadol/paracetamol, trimetazidine, valsartan, valsartan/HCTZ,

	venlafaxine
10/14/2015, FDA	FDA added active pharmaceutical ingredient (API) manufacturer Megafine Pharma's (India) to a list of foreign manufacturing sites banned from sending products to the US.
12/23/2015, FDA	Problems with the potency of warfarin made at one plant and Cadila Healthcare (India) agreed to temporarily suspend production
04/12/2016	Several large Indian pharma companies under US FDA scrutiny: Ipca Laboratories Limited, Natco Pharma Limited, Dr Reddys Laboratories, Wockhardt Group, Lupin Pharma, Cadila Pharmaceuticals Limited, Sun Pharmaceutical Industries, Emcure Pharmaceuticals
4/20/2016, FDA	Clinical and bioanalytical studies conducted by Semler Research (India) were considered unacceptable
07/22/2016, EMA	Recommends the suspension of a number of nationally approved GMPs in 29 European countries for which BE studies were conducted at Semler Research Centre Private Ltd (India) • Amoxicillin, atovaquone/ proguanil, celecoxib, duloxetine, ebastine, eletriptan, eprosartan, erlotinib, etoricoxib, irbesartan/ hydrochlorothiazide, pregabalin, rasagiline, rosuvastatin, saquinavir, tramadol/ paracetamol
12/23/2016, FDA	Significant deviations from CGMP for active pharmaceutical ingredients (API) at Wockhardt Lts. (india), including destruction of original records
03/23/2017, EMA	Recommends the suspension of more than 300 GMPs in 26 countries of the EU coming from from Aurobindo Pharma, Strides Arcolab and Zydus Cadila (India) due to unreliable BE studies from Micro Therapeutic Research Labs (India) • Amlodipine/valsartan, aripiprazole, baclofen, betahistidine, bupropion, carbimazole, carbocisteine, clindamycin, cromoglicate, dicloxacillin, dutasteride, ethinylestradiol/levonorgestrel, etodolac, gliclazide, hydroxizine, ibuprofen, irbesartan, loperamide, metformin, metoclopramide, naproxen, olanzapin, omega-3 fatty acid products, paracetamol, perindopril/indapamide, tadalafil, tianeptine, ursodeoxycholic acid, voriconazol
4/20/2016, FDA	Clinical and bioanalytical studies conducted by Semler Research (India) are unacceptable
06/20/2017, FDA	US bans imports from a division of India's Sun Pharmaceutical Industries (India) due to continued GMP violations
06/23/2017, EMA	Temporarily suspend marketing authorisations for numerous GMPs for which clinical and/or bioanalytical parts of the bioequivalence studies were performed at the Micro Therapeutic Research Labs • Amlodipine/valsartan, aripiprazole, baclofen, bendro-flumethiazide, betahistidine, bupropion, carbimazole, carbocisteine, clindamycin, cromoglicate, dicloxacillin, dutasteride, ethinylestradiol/levonorgestrel, gliclazide, hydrocortisone, hydroxyzine, ibuprofen, irbesartan, loperamide, memantine, metformin, naproxen, olanzapin, omega-3 fatty acid products, paracetamol, perindopril/indapamide, prednisolone, tadalafil, tianeptine, ursodeoxycholic acid, voriconazol

BE: bioequivalence. CGMP: current good manufacturing practice, EMA European Medicines Agency. FDA: Food and Drug Administration. GMPs: generic medicinal products. HCTZ: hydrochlorothiazide. NDEA: N-nitrosodiethylamine. NMDS: N-dinitrosodimethylamine.

Table 5. Recalled cardiovascular generic medicinal products since 2015 by the European Medicines Agency

Angiotensin converting enzyme inhibitors	Fosinopril, ramipril
Angiotensin receptor blockers	Candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan
Antiaplatelet drugs	Clopidogrel, dipyridamole
Antianginal drugs	Trimetazidine
Antibiotics	Amoxicillin, cefaclor, cefpodoxime, cefprozil, cephalexin, cephalexin, cefuroxime, clindamycin, dicloxacillin, phenoxymethyl penicillin
Antifungals	Fluconazole, voriconazole
Anticoagulants	Heparins, warfarin
Antihypertensives	Amlodipine/valsartan, irbesartan/HCTZ, perindopril/indapamide, telmisartan/HCTZ, terazosin, valsartan/HCTZ, valsartan/amlodipine/HCTZ
Beta-adrenergic blockers	Metoprolol, nevibolol
Calcium channel blockers	Amlodipide
Diuretics	Bendroflumethiazide
Fluoroquinolones	Ciprofloxacin, ofloxacin
Glucocorticoids	Dexamethasone, hydrocortisone, methylprednisolone, prednisolone
Glucose-lowering drugs	Gliclazide, glimepidide, metformin, pioglitazone, repaglinide
Immunosuppressants	Tacrolimus
Non steroidal anti-inflammatory drugs	Celecoxib, etodolac, ibuprofen, naproxen, paracetamol,
Opioid analgesics	Tramadol, tramadol/paracetamol
Proton pump inhibitors	Esomeprazole, pantoprazole,
Pulmonary arterial hypertension	Bosentan, taladafil
Smoking cessation aid	Bupropion
Statins	Atorvastatin, pravastatin, rosuvastatin
Other	Omega-3 fatty acid products

HCTZ: hydrochlorothiazide.

Table 6. Some suggestions to fight against low-quality GMPs and improve the confidence on the GMPs

1. The methods and results from BE studies should be routinely made available to physicians, pharmacists and patients • This would allow to make better choices for the patients
2. BE studies should be repeated during the life-time of the GMP, particularly when the manufacturer change the suppliers of the ingredients (active, inactive)
3. GMPs should be dispensed with identification of the manufacturer and distributor and the country of origin in the label
4. Generic pharmaceutical companies should be enforced to: • Register the protocols of BE studies on-line and to publish the results of these studies • Report of incidence of adverse effects • Improve market surveillance
5. Conclusive, reliable and independent evidence is needed to confirm: • The BE between GMPs of the same BD • The efficacy and safety GMPs on "clinical outcomes"
6. The recent increase in recalls, warning letters and adulterated products (related to the presence of impurities or contamination) suggest that it is imperative: • To increase the frequency of inspections of generic pharmaceutical companies and manufacturers (domestic and overseas) at all levels of the pharmaceutical supply chain • To reduce the number of foreign drug facilities without inspection • That both FDA and EMA receive stable funding to perform such inspections and to monitor the quality, efficacy and safety of the thousands of medicines entering in the EU/US • To increase the collaborations between National and International Agencies • To harmonise the international legislation and introduce more drastic measures including law enforcement to criminalise the adulteration or contamination of GMPs and similar offences posing serious threats to public health
7. We need rigorous research to accurately estimate the global burden of substandard (low-quality) GMPs • Information on substandard GMPs should be available to healthcare providers and patients • Governments and drug companies may contribute to the problem by withholding critical information for fear of eroding public confidence on GMPs
8. We need a global strategy that unifies the efforts of all the stakeholders including drug manufacturers, care providers, Governments, health professionals, patients and judicial systems and ensure that only high-quality GMPs are available for use

BE: bioequivalence. GMPs: generic medicinal products.

Figure 1

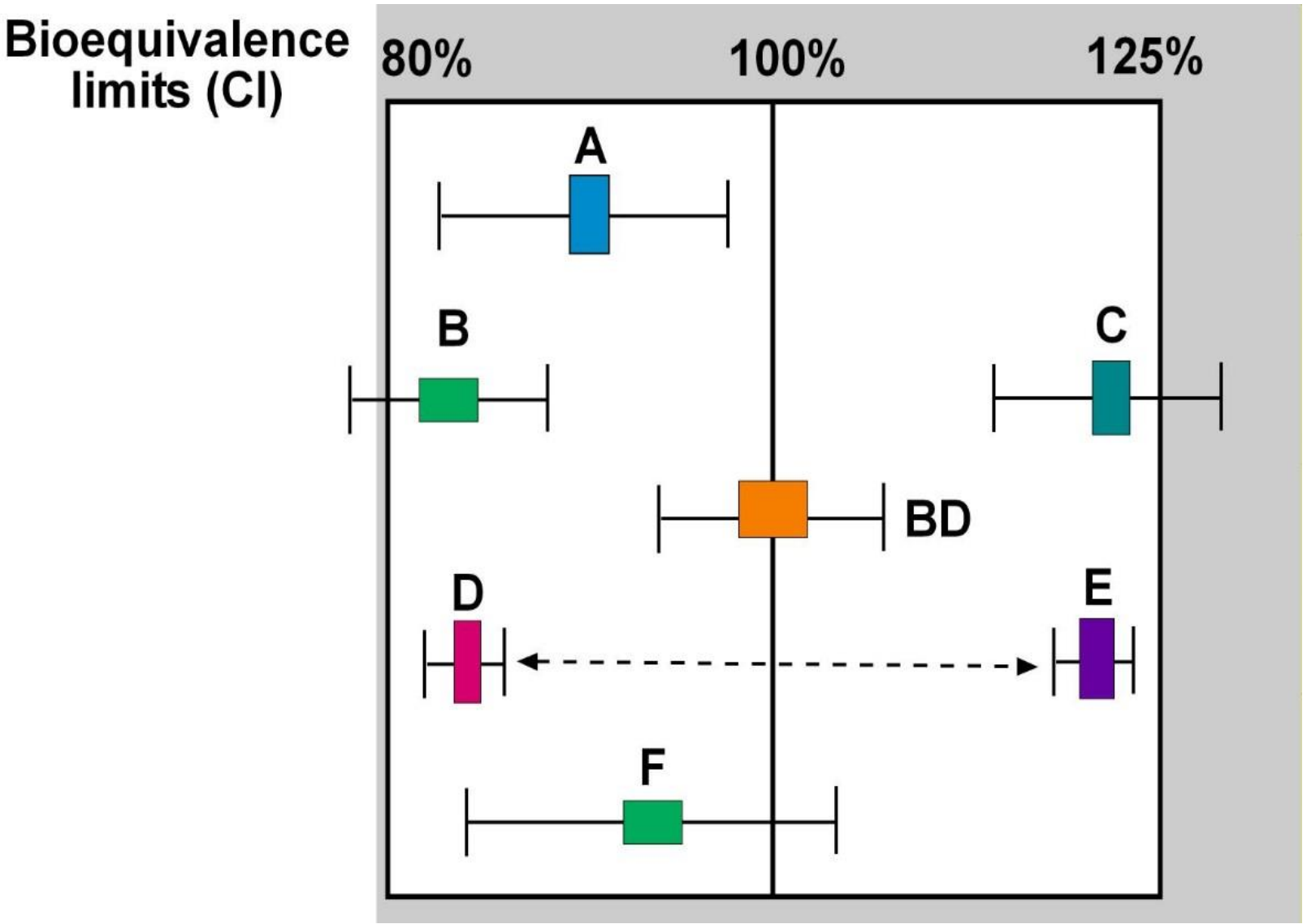

Figure 2

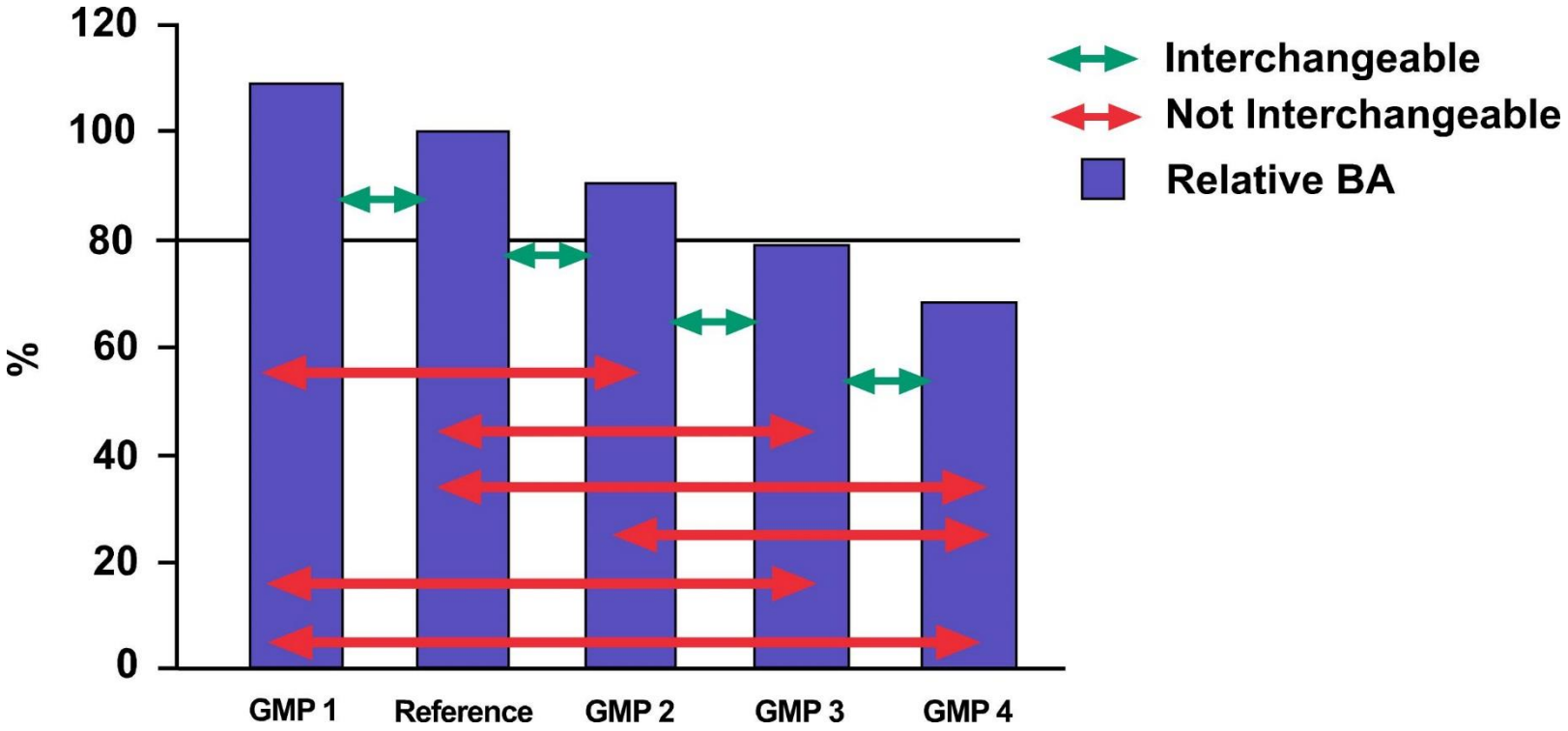

Figure 3