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# BIOEQUIVALENCE: HEALTH, COMMERCIAL AND POLITICAL IMPLICATIONS OF THIS TECHNICAL TOOL

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**Abstract:**
Bioequivalence (BE) is a clinical-pharmacological research method that has acquired great relevance in most of the countries due to its health, commercial, and political importance. Some regulatory agencies require routine BE for all products registered in their national territory, while others opt for policies that require this study only for certain products. The truth is that even today there are current debates about its definition, its clinical relevance and the level of requirements that each country must ask to those companies that aim to register a new product.
The objective of this paper is to provide different perspectives on the concept of bioequivalent drugs, establish what are the advantages or disadvantages of adopting different policies on BE, identify the interests associated with this concept and clarify its real importance for public health.

**Key Words:** Bioequivalence, Kinetics, Substitution, limitations, implications

## INTRODUCTION

Bioequivalence (BE) is a condition that has certain pharmaceutical product in relation to other product, when both of them are considered pharmaceutical alternatives; when, after oral administration, when they have the same molar dose of both products, when their bioavailabilities remains similar (with a certain degree of difference tolerated) and when their effects can be expected to be essentially the same[1,2].
This term (BE), although it can be considered just like a technical concept, it reflects a main importance for health, commercial and political interests.

### What is Bioequivalence?

The term BE is related to pharmacokinetic studies that make it possible to determine whether a pharmaceutical product that is already commercially available in the market (considered as reference) and a similar version of that same active pharmaceutical ingredient (API) that appears on the market

after the first product designed as the "reference listed drug" or "reference product", share basic kinetic attributes after the administration of a single dose, such as reaching the general circulation with the same relative speed, within reasonable limits of difference (each country has the local authority to establish these percentages of difference tolerated for each API or therapeutic group). These studies must be carried out in vivo, in healthy volunteers, administering the commercial product (new brand name product) that wishes to demonstrate bioequivalence with the reference brand, taking bloodstream samples and trying to demonstrate that the new brand is present in the same amount, and it has very similar kinetic parameters of absorption, distribution and elimination as the reference product (Fig.1A). For the BE study, both products must have the same pharmaceutical formulation (tablet, capsule, tablet, etc.).

In other words, been bioequivalent means absence of a significant difference in pharmacokinetic process between two commercial products of the same API, data that indirectly express the rate of drug incorporation into the bloodstream and its contact with the BioPhase, when they are both administrated at the same doses and with similar conditions. Hence, the pharmaceutical company in order to sell its product in the local market must prove that the one is pharmaceutically similar to the brand name version that was already registered and became a "reference product" for that same active pharmaceutical ingredient.

**What is NOT bioequivalence?**

Bioequivalence is not directly related to the concept of efficacy or effectiveness of a drug, since efficacy is inferred only from clinical trials. Nor this term is directly associated with the safety of a product, since this data should be extracted through case-control studies, case series or pharmacovigilance reports.

Therefore, bioequivalence does not refer to the comparison of the safety and efficacy of two pharmaceutical products containing the same API, but is exclusively related to the comparison of the kinetic characteristics of two pharmaceutical products containing the same active substance.

Bioequivalence also does not refer to the comparison of two pharmaceutical products that contain different active substances, even if they are used to treat the same disease or condition.

Furthermore, bioequivalence does not itself guarantee that two pharmaceutical products have the same quality, purity, or stability. These aspects must also be evaluated separately through the design of other types of studies.

**What is bioequivalence for?:**

The BE guarantees consumers the similarities among kinetic parameters of different commercial brands of a same API present on the local market. The demonstration of BE makes it possible that doctors or pharmacists may substitute a drug for another drug, equivalent in terms of composition & dosage.

Substitution of a drug may be necessary for a variety of reasons, such as the availability of multi-source drugs, a specific product that has being out of stock at a pharmacy or the need to switch to a lower-cost drug. In all these cases, the aim BE is to ensure the continuity of the patient's treatment without compromising the quality and safety of medical care when he/she change the trade-mark of that medicine/API.

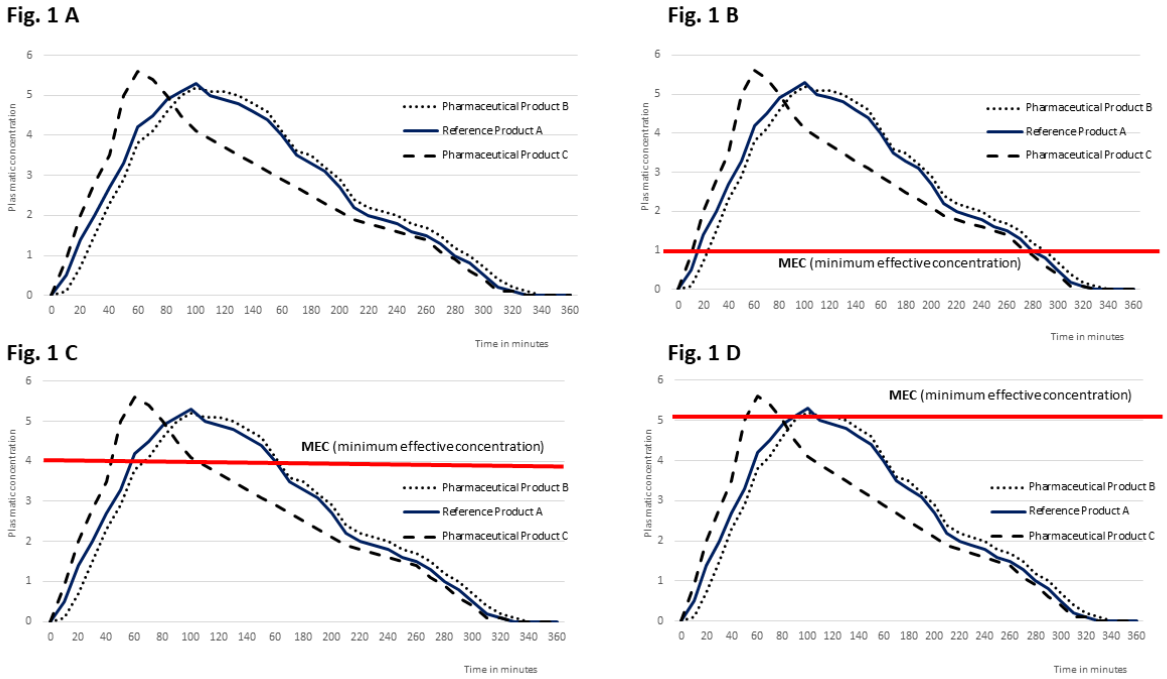
**In what situations BE becomes important?**

For the vast majority of medicines, a small variation in the time to onset of action, or the length of action time, will not be clinically relevant. In figure 1A, it is shown the case of 3 hypothetical trademarks for the same API, one of them has been designated a reference product and the two others are new brands that intend to be registered in the local market to compete with the first product. As it can be seen, all three products are present in the bloodstream from the first few minutes, reaching plasma concentrations between 5 and 6 ug/ml and become practically undetectable in blood after 340 minutes. If the minimum effective concentration of the API would be 1 ug/ml (Fig.1B), then we could assert that all three products begin their action before 20 minutes time with small differences between

them (the reference product A, at 19 minutes, the product B at 15 minutes and product C at 17 minutes). We also can see that products A and B reach a concentration peak of 5.2 ug/ml while product C came up to 5.5 ug/ml, and that all 3 products fall their levels below the effective concentration after 280 minutes. These small differences between the products would not be clinically relevant for most of the therapeutic groups (example: antimicrobials with post-antibiotic effect, analgesics, antiallergy, antacids, antihypertensives, antidiabetics, etc.). However, BE becomes clinically important when small differences counts and expose the patients to a risk when he/she change API`s brand name product after a period of time using another product available in the market. It is for this reason that BE is always justified when the APIs is classified as "high risk" for health, such as anticonvulsants or antiepileptics therapeutical groups, where small variations in kinetic parameters between the different commercial brands might cause plasma levels fluctuations, with periods in which drug concentration may be insufficient to maintain its therapeutic effect, with potential risk of causing seizure. If we look at Fig.1C we can see that product A has a duration of action of 2 hours (period comprised between 40 and 160 minutes), product B will also last 2 hours (period between 42 and 162 minutes), while product C has a duration of action of 90 minutes (period between 25 and 115 minutes). This means that although all 3 products correspond to the same API and even might have the exactly same area under the curve, if the patient was treated with brand A or B products and switched to brand C for any reason (price, availability, convenience, etc.), he/she should know that the drug action will start about 15 minutes earlier than usual and that the interval of dose should be different. In other words, the case shows 3 products for the same API that have a different behavior in kinetic terms, and if these differences of B and C in relation to A exceed 5%, then these new products cannot be considered bioequivalent with A. In a market in which the BE is routinely required for all products, B and C will not be registered or marketed, hence, "A" product will have the pharmaceutical monopoly for this API in that country.

On the other hand, if we know the level of the toxic concentration for that API, like it is shown in Fig. 1D, we can observe that product A and B remains slightly below the TC level, while product C reaches that toxic concentration and remains above that line for about 20 minutes, that is why in this case, product C is not only not BE in relation with A, but also it would not be eligible to be registered, since safer options already exist in the pharmaceutical market (Fig. D).

**Fig. 1.** Bioequivalence of three products for the same active pharmaceutical ingredient



Other situations in which BE could be clinically relevant, even without APIs belonging to the high-risk group, are those in which the pharmacokinetic aspects guarantee minimum plasmatic levels capable of achieving certain effect, and therefore, small variations in the concentrations reached. by the drug (administered in different commercial brands) will modify the possibility of causing a desired effect. For these therapeutic groups, the kinetic parameters should be kept stable and, if possible, people should not vary the product during use. One example of this type of drugs is the immunosuppressive group, where the change of commercial brand could reduce the levels of immunosuppression and eventually make the transplants fail. Another situation where BE might be important is the oral contraceptive group. In recent decades, to avoid the adverse effects of estrogens and progestogens, the amounts of these hormones in marketed products have been significantly reduced at the world trade level. This fact brings as a consequence that small kinetic variations either due to the drug formulation in the way it is commercialize, or due to temporary special situation that patients may have (i.e. diarrhea), have a risk of causing plasmatic levels of the drug that may fall below the minimum effective concentration that is required to prevent ovulation.

Although all these cases are hypothetical, they invite us to think over about those situations where BE has clinical relevance expressing the real potential utility for this concept.

In countries where the BE is routinely required for all API; the Regulatory Agency will demand this study for any product that wishes to be register; hence, the product that was first registered will be declared as RP, and the pharmaceutical company owner of this product will require that the Regulatory Agency demands to the other pharmaceutical companies that wants to register a new trademark of that same API, that submit BE studies carried out with correlation to the designated RP. Then, if the study does not demonstrate similarities in kinetic parameters in relation to first drug registered, it would not be able to be include in the local market due to its discrepancies with the RP. Many local producers, because these BE studies are very expensive or because they take time to be verified by the Regulatory Agency, give up in their intention of presenting its commercial alternatives. That is why, the owner of the RP registered will profit of a monopoly situation of the trade of this API for at least a period of time [3].

**Is BE always necessary for oral pharmaceutical products of the same API in all countries?**

Some Regulatory Agencies, such as the ANMAT of Argentina, do not consider that to demonstrate BE for all API and all pharmaceutical products related to that API. In this case BE is only required for certain therapeutic groups that present a high risk for health or for drug with certain kinetic features that may result inconvenient for those patients that use different trademarks for the same API.

On the other hand, a pharmaceutical product that has already been shown BE with the RP, but that makes changes in the components, excipients, or manufacturing method, must demonstrate BE again in order to assure that this pharmaceutical product continues to be have the same characteristics when compared to the reference product [4].

For International reference agencies like FDA or EMA, bioequivalence concept is very similar to the one described, and refers to the direct experimental comparison between two drug products with the same qualitative and quantitative active ingredient (but not necessarily with similar excipients) performed in healthy volunteers and showing an 90% confidence interval (CI) and an acceptance range of 80-125% of differences [5]. Relevant parameters for the evaluation of BE in these agencies are the total exposure determined by the area under the curve (AUC), the peak exposure or maximum plasma concentration (Cmax), and the time at which Cmax is reached (tmax). The AUC is calculated from the time of administration (t=0) to the last measuring point (AUC0-t) and extrapolated to t=∞ (AUC0-∞). Extrapolation of up to 20% of the AUC0-∞ is accepted by both the US-FDA and the EMA, which means that the sampling schedule should allow the AUC0-t to cover 80% of the AUC0-∞ [6]. Differences between BE criteria in EMA and the US-FDA are the number of studies requested since while the EMA recommends one single fasting BE study, FDA demands one single-dose fasting study just for immediate-release oral solid formulations of Biopharmaceutics Classification System Class I but recommends two BE studies, one fasting- and one fed-state study for both immediate-release and modified release formulations in general. Regarding the expected number of samples to

be taken per subject and dose is explicitly given as 12-18 by the FDA, whereas the EMA only requests a "suitable number of samples" to be taken without mentioning any explicit numbers. Concerning the topic of narrow therapeutic index drugs, the need for narrowing the AUC range is still under discussion at the FDA, while the EMA gives a limit of 90.00-111.11%[7,8]. In relation to the designation of the reference product, even when a certain pharmaceutical company carries out the development and the preclinical and clinical studies, the FDA and EMA have different products for the same API, an aspect that confirms that the designation of the PR is arbitrary and has more to do with the commercial aspect and with the timing and timing of the registration application, than with the scientific-technical aspects.

**Can a product that is not bioequivalent still be registered & marketed?**

Although, it would be desirable for a same API that all its commercial brands were bioequivalent, a product can perfectly be marketed and not be BE with its reference product. It would only be necessary for this situation to be recorded in the package leaflet, so that the patient and his treating physician can take this fact into account, and not change the commercial brand during treatment to avoid fluctuations in API blood levels in those clinical situations where it is important that the patients do not change the brand trademark (immunosuppressors, antiepileptics, etc.).

**What is the difference between BE (Bioequivalence) and BD (Bioavailability)?**

Bioavailability (BD) for a given drug formulation orally administered provides an estimate data of the relative fraction of the dose that is absorbed and arrived to the systemic circulation. In other words, it is the quantity and the speed with which an active ingredient contained in a pharmaceutical formulation, reaches the systemic circulation. This process is reflected by the concentration/time curve or the urinary excretion[1,2].

On the other hand, as already mentioned, BE is the comparison between two oral formulation medicinal specialties after their administration in molar doses to healthy volunteers, demonstrating that they are similar in kinetic terms[2].

**In what situations is it useful to consider requesting a bioavailability study?**

As already mentioned, the BE requires drug administration to a healthy volunteer. However, there are some APIs that can cause serious adverse effects in those people in which they are administered, even when this administration is in a single dose. Therefore, when the drugs are potentially toxic or capable of causing harm to those who receive them, it would be unethical to use them in healthy individuals; this is why, in these situations, BE studies would not be acceptable. This is the case of oral formulation cancer drugs, or others with proven toxicity (i.e. Clozapine). It is in these situations that comparative BD studies in patients could be useful to demonstrate similarity between two pharmaceutical products of the same API.

**Are BE products interchangeable with each other?**

Interchangeability refers to the possibility of performing a therapeutic exchange between two medications. In other words, this term refers to the medical practice that consists on changing one medicine for another, hoping that the same effect will be obtained in a certain clinical situation and in any patient. Therefore, BE does not imply interchangeability, since this last concept is a medical act of the health professional who prescribes the drug. In some countries, such as the Argentine Republic, by Law No. 25649 5, the pharmacists are empowered to substitute pharmaceutical products of the same API without needing to consult the treating physician[9,10] .

The demonstration of bioequivalence is a common regulatory requirement in several countries to guarantee the quality of multisource medicines (pharmaceutical products for the same API manufactured by different manufacturers), however, being BE is not enough to establish interchangeability, since there are other factors. that may affect it, such as the excipient, the pharmaceutical formulation and the manufacturing process.

Bioequivalence also refers to the comparison of the absorption and distribution of the active substance between two formulations of a drug, while interchangeability refers to the ability to switch between different formulations of the same drug without affecting its efficacy or safety. If two drugs are bioequivalent, it means that they are expected to have similar therapeutic effects in the body, however, this does not necessarily mean that they are interchangeable. The interchangeability between medicines can be evaluated through a "switch clinical trial study", that evaluates the efficacy and safety of changing an existing treatment to another treatment.

**Bioequivalence is a fact or a judgment?**

As we previously anticipated, the term BE refers to similarities between certain products with its innovator API. However, how similar must be a product to become bioequivalent? That difference is a range of results the test formulation within 80% to 120% of the reference formulation (20% rule) or within 80-125% range (80-125 rule)[11,12]. The value chosen between these limit points of these ranges is arbitrary established by each local authority and changed during the time and the country that adopted BE policies.

The design of the BE test may also change according to the local authority that might demand a crossover design or different sample size from another Regulatory Agency[13].

The washout period criteria, defined as the time between two treatment periods may also change from country to country[14]. Hence, if limits, criteria, sample size[15] or design of BE studies[16] can fluctuate along the decades time or according to the geographical territories[15-18] where the BE policies are applied, then we can consider that the concept of BE is more a judgment that a fact.

**Had innovator referent products demonstrated better clinical results than new market options or generic products?**

When two formulations of the same drug or two drug products are claimed bioequivalent, prescribers assume that if essentially no evidence of therapeutic failure of bioequivalent products could be found between drugs[19,20], both of them will provide the same therapeutic effect or that they are therapeutically equivalent, and had the same efficacy in their patients[21-23]. However, this statement is not true because, only clinical trials that are chose as the endpoints of the study comparative efficacy or safety are able to demonstrated this point [19-23]. New products of certain APIs that had already a referent product registered in a local market, might be become a “generic” option if its compliment certain items like BE study with referent product for that API, and is registered at a lower price or offer potential benefits for substantial health care cost savings compared to their branded drug counterparts[24,25]. However, generic adoption might be is hindered by doubts among physicians and patients regarding their efficacy and safety[26-28]. Frequently, the argument is that BE no only demonstrates quality manufacture procedures but also reflects the idea that ensures the efficacy and safety of the product. However, neither the original nor the alternative product (whether generic or not) will be able to demonstrate efficacy if they do not perform randomized controlled clinical trials that have that specific goal.

**When can you consider to use a Bioexemption?**

The Bioexemption (BX) is the exemption from performing in vivo bioavailability (BD) and/or bioequivalence (BE) studies for immediate-release solid oral dosage forms based on the Biopharmaceutical Classification System (BCS); when the solid oral formulations to be tested are proportionally similar to another product whose equivalence has already been demonstrated by an in vivo or in vitro study; or for subsequent changes in formulations that do not mean a substantial change in the way of production of a drug that has previously demonstrated BE. According to the BCS classification, all API class I and III can perform BX. It is clear that the advantage of BX is that this test allows to avoid the exposure of healthy volunteers to BE regulatory required studies, and also economically reduce the cost of the registration process of new pharmaceutical products.

**Who is benefited from routinely requesting BE for all pharmaceutical products marketed in a country?**

BE studies are a type of clinical study designed to determine pharmacokinetic equivalence within certain statistical criteria established by each country at the government regulatory level, between a similar multisource product that is intended to be incorporated into the local pharmaceutical market in relation to a reference product already registered. This type of study constitutes a requirement for the approval of multisource products, which have the particularity of improving the accessibility of these drugs to the general population and lowering their costs, due to the fact that in general they tend to have a lower retail public price than the RP.

We have already stated that BE for all commercial brands present in the local market of a same API is desirable. This situation generally occurs in countries that have a generic policy and that demand manufacturers to demonstrate BE with the reference product and register the new product at a substantially lower prices than those that already exist in the market (generic policy).

Among the advantages of having BE studies for pharmaceutical products, it should be added the fact that patients will be able to use any available brand present in the market of that API in its oral formulation, without worrying about the potential differences between them. It is also an advantage that the studies to demonstrate BE are short studies (2 days on average), in which the participating subjects are healthy volunteers, that are in a comfortable situation, in a leisurely environment, with a close monitoring of their health status including a laboratory, serology, imaging studies that additionally constitute a complete health check. It should be noted that a certain number of volunteers who undergo this screening have discovered that they had previously unknown pathologies.

Among the disadvantages or limitations of bioequivalence studies, it should be mentioned those items related to the study subjects (healthy volunteers), and those related to economic aspects and the limitations of the bioequivalence process itself. Regarding the healthy volunteers, exist controversial ethical aspects related to their submission to adverse events due to the administration of a medicine that he/she do not need, without obtaining any benefit in the case of bioequivalence studies, except for knowing their state of health, and the payment of per diems. An example of this is the API Clozapine. The presence of adverse events in healthy volunteers participating in these studies has been quantified by a study by Huic et al[29], where 58 bioequivalence studies with 885 participating healthy volunteers were analyzed. It was observed that 115 of them (13%) presented some adverse event, the majority of which were mild, but 14 of them (6.7%) presented severe adverse reactions.

On the other hand, the BE study in healthy volunteers has a high market price that companies must pay. Generally, few laboratories at national level are authorized to carry out these studies, hence, an oligopoly situation is created where the values are agreed and where national manufacturers are demand to pay a very high price. This situation pushes small national companies to the decision to choose not to register their products in the Regulatory Agency or if they do, they will transfer their cost to the price of the products that are introducing into the market, hence, BE becomes an economic barrier for small national producers.

**Limitations of Bioequivalence Studies**

Among the limitations of bioequivalence studies in their pharmacokinetic aspects, it should be noted that these are studies carried out in healthy volunteers, where the pharmacokinetics might differ from patients affected with a certain pathology. It is clear that the kinetics under disease conditions vary substantially, therefore BE data in healthy volunteers are not 100% transferable to individuals holding certain diseases.

Noteworthy, therapeutic equivalence is often subrogated to the pharmacokinetic equivalence reported in BE studies, which is a mistake since one concept should not be transferred to the other since they are wide different principles.

Among other limitations of bioequivalence studies are, for example, that the concentrations used for certain APIs, are not always those that are later used clinically, such as in the case of API Lamotrigine. It is because of this situation that usually lower concentrations of the same pharmacologically active ingredient are generally bio-excepted for demonstrating proportionality with the higher concentration.

An additional fact that must be taken into account is that the declaration of bioequivalence informs us that the test product and the reference product have reached "similar" plasmatic concentrations within a pre-established statistical criterion. As previously mentioned, the similar plasmatic concentration "subrogates" the biophase concentration of the test product (where its dosage may not be feasible). However, it may be possible that for some APIs, new brand products are bioequivalent to the reference product and yet exist reports of lack of efficacy in pharmacovigilance systems. The above situation could be explained by a pharmacodynamic mechanism, that is, the interaction of the test drug with a certain receptor or pharmacological target different from that of the reference product, which results in a lack of efficacy or different pharmacological action of the API [30-34].

**Discussion**

The BE represents for an oral formulation of pharmaceutical products that intends to be registered and commercialized in a national territory, a parameter of similarity with another product previously registered in that country, and that it has been considered as reference product for that same active pharmaceutical ingredient. A product that demonstrates bioequivalence assures consumers of this drug that one brand or another is similar enough to take one or the other indistinctly. In other words, the concept of BE is kinetic, and it is not directly synonymous with whether the drug is effective or safe.

The BE is then a clinical pharmacology study that guarantees quality in terms of manufacturing similarity and kinetic parameters between the marketed products, and that therefore benefits consumers since all the commercial brands for the same API for oral presentation will be similar in regarding their speed of absorption, distribution and elimination and therefore, any of them will behave in a similar way in relation to these parameters.

However, the decision to demand BE to all products, beyond these supposed health advantages; has strong commercial or political implications. First, healthy volunteers will be submitted to potential risks just to meet business and commercial goals. Second, BE requires costly studies that might discourages potential competitors in the market (small local pharmaceutical industries, cooperatives, public drug production) from developing, producing and registering their own products, in order to serve as alternatives to the first trademark for that same API that was first registered or that was designated as the reference product (usually much more expensive than the other products). Likewise, in situations in which countries have little capacity for the local drug production and their internal market depends on imports, requiring BE means that health financiers will only be able to import those commercial brands that have demonstrated similarity to a RP, thus limiting their purchasing options to certain products, which is not always the most convenient situation from the economic point of view.

This work clearly shows that BE is a highly technical element that has externalities and health and commercial implications that deserve to be analyzed before deciding whether or not to require this type of study for all brand products that wish to be marketed in certain territories.

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**Conflict of interest statement**

Authors declare no conflict of interest.

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