PHARMACEUTICAL EQUIVALENCE OF GENERIC ESSENTIAL DRUGS

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The use of multisource essential drugs widely contributes to the accessibility to health care for populations in difficulties in developing countries or in case of emergency aids. The issue of bioavailability questions the simplistic theories about drugs interchangeability. Bioequivalence studies must be carried out to ensure the therapeutic equivalence of two pharmaceutic equivalent drugs. However, by looking at drugs circulation around the world, one realizes that these studies are not systematically carried out. National regulations set the conditions for the execution of bioequivalence studies but there is no consensus between the various European States. The subsequent deregulation generates even more confusion in the supply of drugs to developing countries. This study consisted first of reviewing a few national regulations and second of considering, on a case by case basis, possible exemptions from bioequivalence studies for active ingredients.

Keywords: Humanitarian aid — Supply — Multisource essential drugs — Generic — Bioavailability — Bioequivalence — Exemption — Quality.

The concept of essential drug was defined in 1975 in order to help developing countries to find their way through the complex supply range from western countries (today, there are about 8,000 specialities in France and more than 15,000 in Germany). As drugs were supplied from many various sources, physical and chemical controls were rapidly established, and highlighted numerous unfortunate cases. This kind of control, though unanimously accepted by members of Public Health and humanitarian organisations, does not solve the problem of interchangeability of multisource or generic drugs.

In the case of the registration of generic drugs on the European market, regulations demand for bioequivalence studies to be carried out when required. Healthy humans are submitted to these tests. The tests are very expensive and not systematically carried out, and the criteria that allow their exemption vary from one country to the next. This might create problems for mutual recognition of registrations within the European Union.

In addition, purchasers from developing countries only occasionally call for bioequivalence studies. This is due to the fact that the technical specifications of tenders often prevent pragmatic attitudes towards these studies.

After defining the specifications of the drugs used, we compared the main national regulations in a non-exhaustive way. Our study was based on national lists of active ingredients and essentially consisted of giving our opinion, i.e. on a case by case basis, either supporting an exemption from bioequivalence studies or, on the opposite, stressing their importance.

As an alternative, we then looked at the kinetics of dissolution, their relevance and limits.

I. CARE ACCESS AND BIOEQUIVALENCE

1. ESSENTIAL DRUGS

In order to allow access to health care for everyone, developing countries (within the context of their national pharmaceutical policies) and humanitarian organisations rely on the essential drugs list drafted by the World Health Organisation (WHO).

The essential drugs list, made of under 400 molecules, is regularly reviewed by the WHO. It is used as a standard by the countries who from there identify their own priorities and make their own selection. An essential drugs list must cover the majority of health problems (80 to 90%) that require medical treatment for people living under normal conditions. The therapeutic and economic criteria used to select basic drugs means that most of them are available as generic drugs [1].

The ninth list of basic drugs (December 1995 [2]) is made of several therapeutic classes as shown in *table I*. A new edition is currently ready for publication.

2. GENERIC DRUGS

A generic drug may be defined as a copy of an original medicinal drug for which production and marketing have been made possible by the expiration of the protection accorded by the patent of the intellectual property covering the active ingredient.

Table I - Therapeutic classes of essential drugs list [2].

Therapeutic classes	Number of molecules	Therapeutic classes	Number of molecules
Anaesthetics	13	Disinfectants and antiseptics	4
Analgesics, antipyretics, NSAI and drug used to treat gout	8	Diuretics	5
Anti-allergic drugs and drugs used in anaphylaxis	5	Gastro-intestinal drugs	12
Antidotes and other substances used for treatment of intoxications	13	Hormones, other endocrine drugs, contraceptives	24
Anti-epileptics drugs	9	Immunological products	25
Anti-infective drugs	76	Muscle relaxants and cholinesterase inhibitors	5
Antimigraine drugs	4	Ophthalmologic preparations	11
Antineoplasics, immunosuppressive and drugs used in palliative cares	22	Ocytocics and antiocytocics	3
Antiparkinsonism drugs	2	Dialysis solutions	1
Drugs affecting the blood	9	Psychotherapeutics drugs	7
Blood products and blood substitutes	5	Respiratory tract	7
Cardiovascular drugs	24	Solution correcting water, electrolyte and acid-base disturbance	9
Dermatological drugs	47	Vitamins and minerals	10
Diagnostic agents	7		

The concept of copy is defined by general texts (Directive 87/21 of 22 December 1986) and by French law (article R. 5133-1 of the Code de la santé publique [3]) by the terms “speciality essentially similar”, that is to say presenting:
- the same qualitative and quantitative composition of active ingredients,
- the same pharmaceutical form,
- if the case arises, bioequivalence with the original product shown by means of appropriate bioavailability studies.

The legal definition of generic drugs was made in France after a decree on health expenditures was promulgated and ratified on 24 April 1996 by the Council of Ministers [4]: “The definition of a generic speciality of another speciality is a speciality that has the same qualitative and quantitative composition of active ingredients, the same pharmaceutical form and which bioequivalence has been determined by the appropriate bioavailability studies; the different oral pharmaceutical forms for immediate release are here considered to be the same similar pharmaceutical form.”

The decree dated 13 March 1997 (article R. 5143-9) defines the scientific criteria that allow exemptions from bioequivalence studies [5]. These criteria will be further exposed.

3. MULTISOURCE DRUGS

The WHO prefers the concept of multisource drugs which are equivalent drugs from a pharmaceutical point of view, but not necessarily from a therapeutic point of view. Multisource drugs that are therapeutically equivalent are interchangeable.

Drugs are pharmaceutically equivalent if they contain the same amount of the same active ingredient(s) in the same pharmaceutical form, if they follow similar or comparable standards and if they are intended to be administered through the same route.

Two drugs are therapeutically equivalent if they are pharmaceutically equivalent and if appropriate results of studies (bioequivalence studies, clinical or *in vitro* pharmacodynamic studies) show that after administration of the same molar dose, their effects, both those concerning their efficacy and safety, are essentially the same [6].

4. QUALITY OF ESSENTIAL MULTISOURCE DRUGS

Due to the specificity of their registration, the quality of a generic or a multisource drug depends on the following three criteria :
- quality of raw material
- stability studies
- bioequivalence studies

Problems of raw material and stability are the most common. They are indeed easily detected with physical and chemical methods.

According to ICH (International Conference on Harmonisation), bioequivalence is the third criteria of quality as it is indirectly related to efficacy [7].

5. BIOAVAILABILITY, BIOEQUIVALENCE AND ESSENTIAL DRUGS

Bioavailability means “the rate and extent to which the active ingredients are absorbed by the body from a pharmaceutical form and become available at the site of action” and bioequivalence means “equivalence of bioavailabilities”.

Two medicinal products are bioequivalent if they are pharmaceutical equivalents or alternatives and if their bioavailabilities (rate and extent) after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

The bioavailability of an active ingredient globally depends on intrinsic factors (granulometry, polymorphism, solubility, rapidity of dissolution, level of purity, etc.) and outside factors (manufacturing adjuvant, manufacturing and storage conditions, characteristics of the packaging of the finished product), not to mention the interpersonal variations among patients.

In any case, for equivalent pharmaceutical drugs to be considered as interchangeable, they must prove equivalent in a therapeutic point of view.

Various methods can be proposed [6]:
- comparative bioavailability studies (bioequivalence) on human, which consist in measuring a dose of active ingredient or one or several of its metabolites in an accessible biological liquid like plasma, blood or urine,
- comparative pharmacodynamic tests on human,
- comparative clinical tests,
- *in vitro* dissolution tests,

The idea of open international tenders favours competition and thus helps to enhance the accessibility to drugs. However, its main drawback is that it actually widely disregards the notion of quality and a simple *a posteriori* quality control is often considered satisfying though it can lead to fake securities.

Today, the most important issue as far as drugs supplies are concerned is the awareness of quality problems. This must be reached at the developing countries' national policies level and in the various humanitarian programs for medico-pharmaceutical aids.

In terms of bioequivalence, one should clearly follow a pragmatic approach. First, by doing an inventory of the regulations. Second, by drafting a list (out of the tablet and capsule forms of the active ingredients listed on the essential drugs list) of the products that imperatively need a bioequivalence study and the ones for which an exemption from these studies may be accepted.

II. INVENTORY OF REGULATIONS: NATIONAL REGULATIONS

National regulations regarding generic drugs sometimes recognize the possibility of an exemption from bioavailability studies. However, approaches of the selection criteria do vary. *Figure 1* outlines several regulations. Two types of concepts have been itemised. First, general concepts for which exemption is mainly based on the pharmaceutical form or on the risk of bioinequivalence. Second, more specific concepts for which the possibilities of an exemption are based on each different kind of active ingredients.

1. GENERAL CONCEPTS

The legislation in these countries (more and more numerous) means opening the door to exemption from bioequivalence studies, generally without separately looking at each active ingredient.

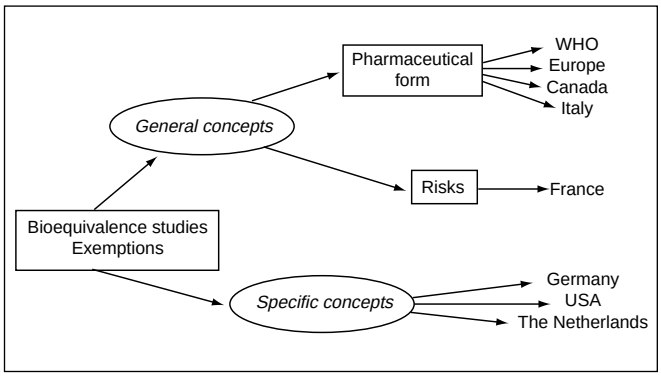

Figure 1 - Different exemption policies for bioequivalence studies.

1.1. According to the pharmaceutical form

These concepts deal with the risks of bioinequivalence according to pharmaceutical forms.

1.1.1. Europe [8]

The European Community has listed recommendations that allow an exemption from bioequivalence studies. There is however no consensus between the various national authorities with regards to their execution.

Criteria for exemption

Bioequivalence studies are generally not required for:
- products which are different from the original product only by the dosage and which the pharmacokinetic is linear, the qualitative composition is the same, the active ingredient/ excipient ratio is the same, if both products are produced by the same manufacturer, if at least one of the dosage of these products has undergone bioavailability and bioequivalence tests and if the results of the *in vitro* dissolution tests are similar under the same conditions;
- slightly reformulated products;
- products intended to be administered through the parenteral tract and containing the same active ingredient and the same excipients;
- orally administered solutions containing the same active ingredient and the same excipients;
- orally administered solutions containing the same active ingredient and the same excipients, with no risk of modification of the absorption;
- products for which an *in vitro/in vivo* correlation with the original product has been proved.

Bioequivalence studies are generally not required for simple solutions of an IV use and for local action products with no systemic action.

Obligation criteria

Bioequivalence studies must be carried out on all new products presented as pharmaceutically equivalent to a reference product if there is a risk of bioinequivalence or a risk as far as the expected therapeutic effect is concerned.

The following forms must undergo bioavailability studies :
- orally administered forms with an immediate release and a systemic action intended for serious indications, and/or with a narrow therapeutic margin;
- products for which the pharmacokinetics are complicated by a weak absorption (< 70%) , a non-linear kinetic or an important presystemic elimination (> 70%);
- substances presenting unfavourable physical and chemical properties (instability, low solubility, etc.);
- non-orally administered forms with immediate release;
- systemic action forms with a modified release;
- products described as presenting problems of bioavailability.

Products for which there is a risk of suprabioavailability (a bioavailability superior to the reference product) must also undergo bioavailability studies in order to reduce the dosage if need be.

Great-Britain and Australia have adopted these criteria as national regulations [9, 10].

1.1.2. The WHO [6]

The WHO has drafted a list of recommendations that allows the exemption from bioequivalence studies or on the contrary their obligation.

Criteria for exemption

They basically apply to drugs that are intended to be administered through the parenteral tract (IV, IM, SC, etc.) in aqueous solution; drugs in orally administered solutions; powdered drugs intended to be reconstituted in solution; medical gas and drugs for auricular, ophthalmic and topical uses and products for inhalation and spraying.

Tablets and capsules are often questioned and interpreted. Yet, texts show that the equivalence can be proved, in some cases, by an *in vitro* dissolution test. This possibility may concern:
- drugs with fast dissolution kinetics;
- drugs with various dosage, with a same formulation produced by the same manufacturer when:
  - the qualitative composition of the various dosages is basically the same,
  - the active ingredient/excipient ratio is mainly identical for all dosages,
  - a bioequivalence study has been carried out on at least one of the dosages;
- in the case of systemic action drugs, if studies show that the pharmacokinetics was linear throughout the whole therapeutic field.

Obligation criteria

Except for the previous described cases, it is advisable to ratification authorities to demand a proof of equivalence. This proof consists of comparing the product to the reference drug. This recommendation concerns:
- orally administered products with an immediate release and capable of systemic action, when one or several of the following criteria apply:
  - drugs recommended for a serious state of health that requires a guaranteed therapeutic efficacy,
  - narrow therapeutic range,
  - pharmacokinetics complicated by a complete absorption, elimination or a high metabolism at the time of first passage,
  - unfavourable physical and chemical properties,
  - widely-known problems of bioavailability,
  - high proportion of excipients in relation to the active ingredient;
- products with a systemic action that are not intended to be administered orally;
- products with a modified release;
- associations in fixed proportions that have a systemic action;
- products with a systemic action that are not in a solution form.

The concept of bioequivalence does not fit to this type of product. The equivalence must be proved through comparative clinical or pharmacodynamic tests.

These recommendations from the WHO aim at setting the limits that should not be overstepped with regards to bioequivalence.

1.1.3. Italy

Criteria for exemption

Italian regulations also admit possibilities of an exemption from bioequivalence studies for drugs with an IV or IM administration, aerosols, drugs for topical use without any systemic action and drugs intended to be administered orally in solution form or in tablet form intended to be made soluble before absorption (effervescent).

Obligation criteria

According to the new regulations, any other form of pharmaceutical presentation must be submitted to bioequivalence tests against the reference product. Drugs registered under the previous regulations do not however need to undergo bioequivalence tests.

1.1.4. Canada [1]

Today, the bioequivalence of a drug must be proved when it is thought that it has not been commercialised in Canada long enough and in sufficient amounts to ensure its innocuity and its efficacy.

Bioequivalence can be proved by comparative bioavailability tests, or by clinical tests. Scientific criteria similar to the ones of the European Community and Australia have been set up to decide when the bioequivalence of drugs that are not considered as new must be proved *in vitro.*

1.2. According to the risk

In this case, the exemption from bioequivalence studies takes into account the risks for the patient, in terms of risk of a decreasing efficacy of the treatment or risk of bioinequivalence.

1.2.1. France

The definition of generic drugs in article L. 601-6 makes provision for the scientific criteria that can justify an exemption

from bioavailability tests. Thus, France distinguishes itself from European recommendations.

Criteria for exemption

These criteria are itemised in decree No. 97-221 [5]. The exemption from bioavailability studies is submitted, for each case, to the director of Afssaps (Agence française de sécurité sanitaire des produits de santé). A speciality can be exempted from bioavailability studies if it is produced by the same manufacturer in the same plant and if its file is a duplicate of the file of the reference speciality. Other cases of possible exemption from bioavailability studies: drugs for which the bioavailability cannot be different from the reference speciality; drugs for which the active ingredient (as far as its toxicity and specific requirements are concerned) should not reveal differences in terms of therapeutic efficacy or side effects. For solid oral forms, *in vitro* dissolution comparison tests must show the equivalence of their dissolution.

As far as the exemption from bioavailability studies is concerned [11], French regulations consider the drug from the point of view of its therapeutic efficacy and of its risks. *Table II* sums up the possibilities for exemption.

Table II - Exemption of bioequivalence studies according to Afssaps.

		Bioinequivalence	Risks
		Possible risk	Exluded risk
Therapeutic risks	Possible risk	no	no
(efficacy or side effects)	Excluded risk	no	yes

Yes: exemption of bioequivalence study can be possible. No: exemption of bioequivalence study can not be possible.

Obligation criteria

Bioequivalence studies are imposed when at the same time:
- specialities may be bioinequivalent,
- therapeutic and/or side effects closely depend on the time related amounts of active ingredient released in the body.

2. SPECIFIC CONCEPTS

Regulations in other countries have adopted other criteria as far as the exemption from bioequivalence studies is concerned: criteria that are inherent to the pharmaceutical form and criteria that are linked to therapeutic risks of active ingredients on a case by case basis. Lists of active ingredients for solid oral forms have been set up. These lists itemise either the substances exempted from bioequivalence studies or the ones which have to be submitted to tests.

2.1. Germany [12-16]

The bioavailability commission of the Federal Institute for Drugs and Medical Devices has listed the active ingredients that do or do not require a bioavailability study. This list only deals with orally administered active ingredients with an immediate release. Each substance shows its content, its salts, its esters.

Criteria for exemption

Bioavailability studies may not be essential for oral forms administered in solution, providing that the excipients do not modify absorption. They are also not essential for solid oral forms with an immediate release.

Obligation criteria

In Germany, bioavailability studies are generally required for oral forms with a modified release, but also drugs administered through the rectal or vaginal tracts, preparations with a topical use with systemic passage, preparations intended to be absorbed by the respiratory or oral mucous membrane, IM or SC injectable preparations, except for aqueous solutions.

The following active ingredients presented in immediate release oral form are generally submitted to bioavailability studies: antiarrhythmic, antidiabetic, antiepileptic, anticoagulant, drugs with an anti-infectious action, broncho-dilatators, cardiac glucosides, substances with an hormonal effect.

2.2. The Netherlands

Criteria for exemption

The Netherlands also accept that a certain number of substances in conventional pharmaceutical forms for oral administration may not create bioavailability problems.

Therefore, the college considers that it is not necessary to carry out a research for biological bioavailability for the registration of orally administered drugs with an immediate release and containing one of the active ingredients in question.

Obligation criteria

Modified release forms must be submitted to bioavailability tests, like solid oral forms containing a substance that does not belong to the described list.

2.3. United States [17]

Criteria for exemption

The FDA (Food and Drug Administration) thinks of the possibility for an exemption from bioequivalence studies for:
- parenteral solutions for an IV administration, only if they contain the same active or inactive substances and in the same concentration,
- preparations for a topical use with no systemic effect,
- unabsorbed orally administered preparations,
- products for inhalation,
- products in solution forms when administered orally.

Moreover, the FDA makes it clear that the described possibilities for an exemption are only valid for specific indications of the Drug Efficacy Study.

Obligation criteria

The FDA has listed the active ingredients known as problematic as far as the bioavailability is concerned and which therefore need bioequivalence studies. This list includes active ingredients like antiarrhythmics, anticholinergics, antiepileptics, antihypertensives, diuretics, anti-infectives, antineoplasics,

bronchodilatators, cardiotonic glucosides, corticoids, hormonal action products.

The substances which are not on this list are submitted to individual tests in order to determine if they should or should not undergo bioequivalence tests.

3. DISCUSSION

This inventory of regulations shows that the requirements for the exemption from bioequivalence studies of a pharmaceutical product differ from one country to the next. A few differences remain, even for the most general concepts that consider the pharmaceutical form or in terms of risk for the patient:

- the forms for a parenteral use for example: the WHO and the European legislation exempt any kind of forms for parenteral use from bioequivalence studies. The Italian legislation only exempt from bioequivalence studies the forms that are intended to be injected in IV or IM injections. In fact, for forms administered in subcutaneous injections, there is a real absorption phase that can thus directly have an influence on the bioavailability;
- we can also notice various interpretations as far as aerosols are concerned. The WHO and Italian regulations exempt aerosols from bioequivalence studies, whereas European regulations only exempt medical gas from bioequivalence studies.

III. THE STRATEGY OF THE CHMP: SOLID ORAL FORMS FROM THE ESSENTIAL DRUGS LIST

The Centrale Humanitaire Médico-Pharmaceutique (CHMP) has authority to supply non-profit making organisations with essential drugs, medical equipment and laboratory reagents.

As far as essential drugs are concerned, its main mission is to stock up with drugs at the best price and make sure of their quality, especially with the help of its control laboratory.

As a supplying organization with a strictly humanitarian aim, CHMP is confronted to two kinds of problems.

First, CHMP faces contradictory situations at tenders level: while some demand bioequivalence studies on every single drug, some do not require any. The wording of those tenders shows the lack of knowledge of the issuers of the tenders regarding the reality of the market. CHMP wants to lay stress on the importance of "price-efficacy-risk" issue, without which tenders tend to be devoid of interest. It is important to act with discernment when it comes to products that may present bioavailability problems and with products known for their easy absorption and rapidly maximal bioavailability. Today, it is important to clarify the notions of interchangeability and bioequivalence of multisource drugs. Bioequivalence is especially important in the case of the use of antibacterial and antiparasitical drugs. In these cases, insufficient bioavailability could mean inefficacy such as resistance to treatments, a situation that would plunge the nursing team into a state of utter confusion.

In the case of generic or multisource essential drugs, a bioequivalence study is obviously the best way to show interchangeability and therefore efficacy. Unfortunately, this study is not always carried out on drugs that are intended to be sent to developing countries. Indeed, these drugs are found in the supplies of most open tenders and this for three intimately linked reasons:

- such studies are very expensive in Europe and highly increase drug prices. This situation leads to a potential reduction of drug accessibility and also to less price competitiveness. The requirements of some tenders do indeed favour low prices against quality;
- international tenders maintain a constant pressure on prices reduction and on the deregulation of the market for raw materials which are often of varying quality. Because of the influence of the quality of raw materials on bioavailability, manufacturers hesitate to perform bioequivalence studies;
- drugs for which this kind of study could be replaced with an *in vitro* dissolution study are not clearly specified. Moreover, there is no international consensus between various regulations.

The second kind of problem concerns the physical and chemical quality of the drugs. The multisource drugs market is international, therefore regular controls should imperatively be carried out. It is indeed difficult for manufacturers to rely on a constant supply of raw material. The control laboratory of CHMP systematically checks the drugs that are bought. Most of the found non-conformities concern dissolution tests. The dissolution of the active ingredient is in fact an essential factor of its absorption and it is therefore a parameter that is closely linked to bioavailability.

The WHO stipulates that *in vitro* dissolution tests may be useful to show the equivalence between two multisource drugs. It is however advisable to use this test as rarely as possible and especially not as the unique proof for capsules and tablets, the two pharmaceutical forms for which the dissolution test mainly applies. Solid oral forms represent the higher percentage of the pharmaceutical forms used for humanitarian aid. Therefore, the dissolution test remains essential in evaluating the bioavailability of an active ingredient.

1. THE POSITION OF CHMP TOWARDS BIOEQUIVALENCE STUDIES [6, 13, 17, 18]

Thanks to its experience, CHMP can evaluate the various legislations with regards to bioequivalence and therefore adopt a clearer position.

Table III lists the active ingredients available in solid oral forms with an immediate release which can be exempted from bioavailability studies according to CHMP. *Table IV* lists the active ingredients in a pharmaceutical form which must prove bioequivalent to the reference product.

For solid oral forms with an immediate release, CHMP considers the criteria listed in *table V* to give a ruling on the obligation or the exemption from bioequivalence studies.

When a judgement on the necessity or not of bioequivalence studies is passed, there are three different scenarios:

- when national lists agree: we have considered the option of national legislations agreeing to clearly exempt or to make bioavailability studies obligatory;
- when national lists disagree: some active ingredients are exempted from bioequivalence studies for a particular national

Table III - Active ingredients exempted of bioequivalence not study by CHMP [1, 12-16].

INN	Form	Bioav. USA	Bioav. Netherlands	Bioav. Germany	Bioav. Canada
Acetylsalicylic acid	Tablet	no		yes	
Albendazole	Tablet				
Ascorbic acid	Tablet	no			no
Al-Mg hydroxid	Tablet	no			no
Chlorphenamin	Tablet	no		no	no
Cimetidin	Tablet			no	yes
Clonazepam	Tablet				
Codein	Tablet	no		no	
Diazepam	Tablet		no	no	yes
Diethylcarbamazin	Tablet				
Diloxanid	Tablet				no
Ergocalciferol	Capsule	no			
Ergotamin	Tablet	no		yes	yes
Ethosuximid	Tablet				
Ferrous sulfat+folic ac.	Tablet	no			no
Ferrous sulfat	Tablet	no			
Sodium fluorure	Tablet				
Folic acid	Tablet				yes
Calcium folinat	Tablet				
haloperidol	Tablet			no	yes
hydrochlorothiazid	Tablet	yes		no	
hyoscin butylbromid	Tablet				
Ibuprofen	Tablet			no	yes
Indometacin	Capsule	yes	no	no	yes
Levamisol	Tablet				yes
Loperamid	Tablet				
Mebendazol	Tablet				yes
Metoclopramid	Tablet				yes
Multivitamin	Tablet			no	
Niclosamid	Tablet				
Nicotinamid	Tablet	no			no
Nitrofurantoin	Tablet				yes
Paracetamol	Tablet		no	no	no
Phenobarbitone	Tablet	no			no
Piperazin	Tablet				no
Promethazin	Tablet			yes	
Propylthiouracil	Tablet	yes		no	
Pyrantel	Tablet				
Pyridostigmin	Tablet				yes
Pyridoxin	Tablet	no			no
Retinol	Capsule				no
Riboflavin	Tablet	no			no
Sulfadimidin	Tablet				
Thiamin	Tablet				
Tramadol	Tablet			no	

No: bioequivalence studies exempted. Yes: bioequivalence studies obligatory.

Table IV - Active ingredients for which bioequivalence study is obligatory for CHMP [1, 12-16].

INN	Form	Bioav. USA	Bioav. Netherlands	Bioav. Germany	Bioav. Canada
Acetazolamid	Tablet	yes		yes	yes
Nalidixic acid	Tablet	yes			yes
Aciclovir	Tablet				
Allopurinol	Tablet			yes	yes
Amilorid	Tablet			no	yes
Aminophyllin	Tablet	yes			
Amitriptylin	Tablet			yes	
Amoxicillin	Capsule	yes	no	yes	yes
Arthemeter	Tablet				
Atenolol	Tablet			yes (cardiovasc.)	yes
Atropin	Tablet				
Azathioprin	Tablet				yes
Benznidazol	Tablet				
Biperiden	Tablet			yes	yes
Captopril	Tablet			no	yes
Carbamazepin	Tablet				yes
Chloramphenicol	Capsule				
Chloroquin	Tablet	no		yes	
Chlorpromazin	Tablet	yes		yes	
Ciclosporin	Capsule				yes
Ciprofloxacin	Tablet				yes
Clindamycin	Capsule				
Clofazimin	Capsule				
Clomifen	Tablet				yes
Clomipramine	Tablet				
Cloxacillin	Tablet				
Colchicin	Tablet			yes	
Cotrimoxazol	Tablet				
Cyclophosphamid	Tablet				yes
Dapsone	Tablet				
Dexamethazone	Tablet	yes			
Digitoxin	Tablet	no			
Digoxin	Tablet	no			
Doxazosine	Tablet				
Doxycyclin	Capsule		no		yes
Ephedrin	Tablet			yes	
Ergometrin	Tablet	no		yes	
Erythromycin	Tablet				
Ethambutol	Tablet	yes		yes	yes
Ethinyloestradiol	Tablet	yes			yes
Etoposide	Capsule				yes
Flucytosin	Capsule				yes
Fludocortisone	Tablet	yes			yes
Furosemid	Tablet			yes	yes
Glybencalmid	Tablet				
Griseofulvin	Tablet	yes		yes	
Hydralazin	Tablet	no		yes	
Isoniazid	Tablet	no			yes
Isosorbid dinitrate	Tablet				yes
Ivermectin	Tablet				
Ketoconazole	Tablet				yes

Table IV - Active ingredients for which bioequivalence study is obligatory for CHMP [1, 12-16] (continuation).

INN	Form	Bioav. USA	Bioav. Netherlands	Bioav. Germany	Bioav. Canada
Levodopa+carbidopa	Tablet				yes
Levothyroxin	Tablet	no			
Litium carbonate	Tablet			yes	yes
Medroxyprogesterone	Tablet				
Mefloquin	Tablet				yes
Mercaptopurin	Tablet				yes
Methotrexate	Tablet				yes
Methyldopa	Tablet		no	yes	
Metronidazol	Tablet				yes
Morphine	Tablet				
Neostigmin	Tablet	no			
Nifedipin	Tablet			yes	yes
Nifurtimox	Tablet				
Norethisteron	Tablet				yes
Norethisteron Ethinylestradiol	Tablet				yes
Nogestrel Ethinylestradiol	Tablet				
Nystatin	Tablet				
Oxamniquin	Capsule				yes
Pethidin	Tablet	no		yes	
Phenoxymethylpenicilin	Tablet		no		
Phenytoin	Tablet	yes		yes	
Phytomenadione	Tablet	yes		yes	
Praziquantel	Tablet				
Prednisolone	Tablet				
Primaquin	Tablet	no			
Procainamid	Tablet				yes
Procarbazin	Tablet				yes
Proguanil	Tablet				
Propanolol	Tablet			yes	yes
Pyrazinamid	Tablet				yes
Quinidine	Tablet	yes			
Quinine	Tablet	no		yes	
Reserpin	Tablet	yes			
Rifampicin	Tablet				yes
Salbutamol	Tablet		no	yes	yes
Spironolactone	Tablet	yes		yes	
Sulfadoxine/	Tablet	yes		yes	
Pyrimethmine					
Sulfasalazin	Tablet	yes		inflam.	
Tamoxifen	Tablet				yes
Tetracyclin	Tablet				
Theophyllin	Tablet				
Thiacetazone	Tablet				
Tolbutamid	Tablet				yes
Trinitrate de glyceryl	Tablet				
Valproique acid	Tablet				
Verapamil	Tablet			yes	yes
Warfarin	Tablet	yes			

Yes: bioequivalence studies obligatory. No: bioequivalence studies exempted.

legislation but not for another one. In that case, we have considered each listed criteria to give a ruling on the appropriateness of the studies. The risk for the patient remains the discriminating criterion;

- when the active ingredients are not itemised on any list: these active ingredients have been submitted to tests, considering each criterion of *table V*. They are generally intended to cure tropical or rare diseases in the developed countries. Thus, they are not to be found in the national list, but on the other hand, they belong to the essential drugs list. That is why we have listed them.

We have taken three examples to illustrate the position of CHMP.

The first example is about chloroquine, an active ingredient used to treat paludism. In the USA, chloroquine tablets are exempted from bioequivalence studies. They are compulsory in Germany, whereas The Netherlands and Canada have not yet come to a decision about the subject. Each criterion of *table V* has been appraised by CHMP:

Chloroquine, a substance with a large therapeutic window, is not described as being problematic with regards to bioavailability. Its indications do not directly affect the vital prognosis. Its absorption is fast and its pharmacokinetics is classical. Moreover, active doses are distinctly superior to 2 mg.

And finally, in case of bioinequivalence, the side effects are slightly increased.

The treatment of an entire population with chloroquine tablets with an insufficient bioavailability would however create an important risk of inefficacy, and especially an induction of resistance to the antipaludism drug. This risk being prejudicial on a large scale, CHMP considers that chloroquine tablets must undergo a bioequivalence study to make sure of their interchangeability.

Indometacin is an anti-inflammatory and non-steroidian substance for standard use. It is listed under capsule form in the essential drugs list. The USA and Canada think that bioequivalence studies must be performed. Germany and The Netherlands consider that the tests are not compulsory.

To take a stand, CHMP refers to the criteria of *table V*. Indometacin, an active ingredient with a wide therapeutic window, is not described as showing special bioavailability problems. It is generally prescribed in high doses for indications that do not affect the vital prognosis. Indometacin shows a classical pharmacokinetic and a fast kinetics of dissolution. In case of bioinequivalence, the risks of an alteration of efficacy and the risks of an increase in side effects are weak.

Moreover, the problem of a mass treatment with risks of induction of resistance does not arise. Thus, CHMP considers that this drug can be exempted from studies.

Finally, let us consider the case of niclosamide which is not listed in any national list. Although it has an antiparasitical action, this active ingredient is hardly absorbed: it has a direct impact on parasites. The systemic passage is thus very weak and does not influence activity in any way. The bioavailability represents the amount of active ingredient in the blood, that's why it can not be measured out.

Therefore, bioequivalence tests are by definition useless.

Table V - Obligation or exemption criteria of bioequivalence studies for CHMP.

Criteria	Exemption	Obligation
Therapeutic margin	wide	narrow
Risk of efficacy modification	weak	high
Well-known bioavailability problems	no	yes
Kinetics of dissolution	fast	slow
Serious indications	no	yes
Pharmacokinetic	classical	complicated
Resistance induction	no	yes
Weak strength (< 2 mg)	no	yes
Product non absorbed	yes	no

2. THE POSITION OF CHMP TOWARDS DISSOLUTION TESTS [6]

In order to guarantee the specificity of an essential drug, i.e. its accessibility for the most destitute people, the exemption from bioequivalence studies may be envisaged for the products which are described in a national legislation as non-problematical with regards to bioavailability.

For solid oral forms, national regulations advocate the use of *in vitro* dissolution tests for development and quality control. Several studies demonstrate the importance of the information given by this test. It can help to synthesize information about the raw material, but also about the formulation and the pharmaco-technical features of the form.

This test may be considered acceptable in the following cases:

- drugs for which *in vivo* tests are not demanded;
- various dosages of the same formulation produced by the same manufacturer in the same plant, when:
  - the qualitative composition of the various dosages is basically the same,
  - the ratio of the amounts of the various excipients is the same,
  - an appropriate bioequivalence test has been carried out on at least one of the dosages of the formulation,
  - the pharmacokinetic is linear on the entire therapeutic range.

CHMP control laboratory compared the kinetics of dissolution of chloroquine multisource tablets, according to the method suggested by the USP. The results are shown in *figure 2*.

Out of six generic drugs tested against their market references, only one shows a dissolution profile that may be perfectly superimposed. Generic No. 5 shows a kinetics of dissolution which profile is clearly inferior to the reference product. This generic is therefore not equivalent to the reference drug with regards to *in vitro* dissolution.

The laboratory also studied the kinetics of dissolution of six sets of generic indometacin capsules against their market references. The results are shown in *Figure 3*.

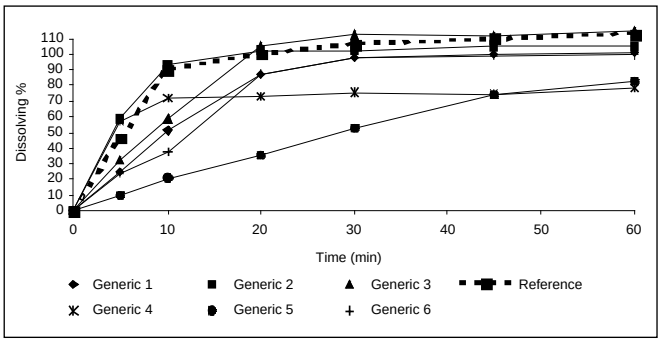

Figure 2 - Dissolution kinetics of chloroquine tablets.

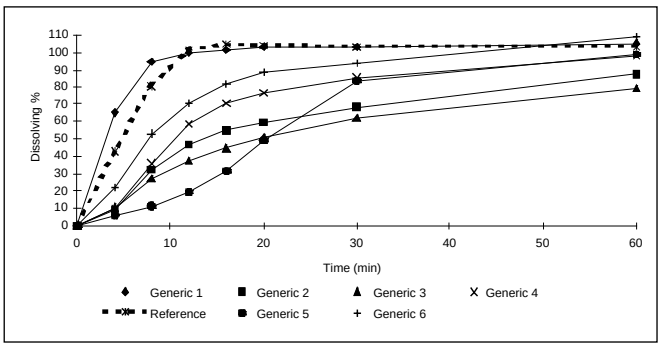

Figure 3 - Dissolution kinetics of indometacin capsules.

As for chloroquine, the profiles of dissolution can not be superimposed. The curve of dissolution of generic drug No. 1 is statistically identical to the reference one. For generic drugs No. 4 and 6, the curves are not statistically different from the one of the reference drugs. After we studied the granulometrical features of the powders contained in the capsules, we were able to reveal that the formulation of the mixing and the granulometrical distribution were two parameters intimately linked with the kinetics of dissolution.

We set that generic drugs No. 1, 4 and 6 had profiles of dissolution comparable to the one of the reference product.

They complied with bioequivalence studies. The dissolution test is thus discriminating enough to highlight differences in formulation. Moreover, it gives a more accurate idea of bioequivalence because there is a correlation between both types of studies. Thus, it is easy to make sure of the equivalence of two drugs through a dissolution test. Indometacin capsules can therefore be exempted from bioequivalence tests.

Let us take a final example: the case of tetracycline capsules for which a dissolution test was carried out according to the conditions of the British Pharmacopoeia. The results are presented in *Figure 4.*

After a granulometrical analysis of every sort of powders contained in the capsules, it was shown that there are huge differences within generic drugs. The dissolution test does not point out those differences. For tetracyclin, it is not discriminating and thus, does not enable one to set an *in vitro*/*in vivo* correlation.

On the other hand, it is possible to make it more discriminating if one modifies the composition of the dissolution medium.

However, playing on the discriminating power of the test in order to achieve better results is something really awkward. Indeed, we would move away from the real *in vivo* conditions and the test would become devoid of interest.

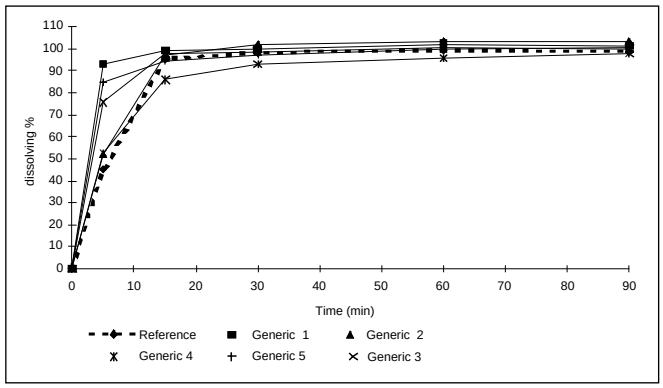

Figure 4 - Dissolution kinetics of tetracycline capsules.

Thus, bioequivalence studies obviously appear to be the only way to determine the equivalence of two tetracyclin capsules.

For CHMP control laboratory, the dissolution test is very useful in order to show the equivalence between two drugs, but must be used with care. Whenever it is possible, the dissolution mediums that are generally used refer to the specific monographs of the pharmacopoeias. They must absolutely not contain more than 5% of an organic solvent in order to respect biological realities as much as possible.

The test must then be carried out in strictly similar conditions. It must show an equivalence of the profiles of dissolution and not only an equivalence of a certain aspect at one time decided by the pharmacopoeias. Indeed, occidental pharmacopoeias do not deal with the dissolution test in the same way. The instrumentation that is used is about to be harmonised between the USA and Europe. The European Pharmacopoeia only decrees general recommendations. The British Pharmacopoeia (BP) describes operating methods for several products. On the other hand, USP is better informed on dissolution tests. However, dissolution mediums, time of sampling and conditions of measurement do vary.

The dissolution mediums used are not standardised yet and they have a direct influence on the discriminating power of the test. It is therefore easy to lower the discriminating property of a dissolution test to show the equivalence of two kinetics of dissolution between two products.

On the contrary, a very discriminating medium can show significant differences between two samples, whereas those variations are not or hardly pointed out in an *in vivo* test. Thus, the problem rests on a possible *in vitro*/*in vivo* correlation that is often not easy to demonstrate.

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For several years and in every country of the world, pharmaceutical authorities have been busy regulating bioequivalence studies.

The evidence has proved that they were not systematically necessary but the relatively recent arrival on the market of very numerous generic drugs increases confusion. The access to health care for the most destitute populations is directly subordinated to the price of the drug, explaining why the

exemption from bioavailability studies could be a favourable factor. However, this exemption must be perfectly mastered in order to avoid taking the risk of administering non-equivalent products to a patient. Our main work has consisted in drafting an inventory of available regulations and it has consisted in proposing an attitude that should be adopted when legislations differ.

At the time of international tenders, technical specifications seldom consider bioavailability issues with enough discernment. Some of them require bioequivalence studies for every product but most of them do not ask for them at all, because inherent problems to this parameter are often misjudged.

According to CHMP, these tenders should be more specific in the technical specifications of the products that must be submitted to bioequivalence studies and the ones that can be exempted from them.

The bioequivalence of generic drugs is an essential key to the efficacy of a treatment. Active ingredients for which the activity specifically conditions the efficacy must absolutely be submitted to bioequivalence studies.

Other active ingredients can be exempted from bioequivalence studies in order to help populations to access health care. There, *in vitro* dissolution tests, if they are used with care, can be sufficient to give a verdict on the equivalence between two drugs.

In Europe, an intra-community legislation is being drawn. This procedure gradually engenders the disappearance of national registration files in favour of multi-national files. This aims at creating better harmonisation. The generic drugs market is international in order to cover everyone's needs. The harmonisation of bioequivalence must therefore take this phenomenon into account.

The multisource drugs market is international and therefore very wide. In terms of quality, the worst can be found next to the best. Information is the best way to point out the risks of the non-interchangeability that may arise.

Through its awarness of the importance of information, CHMP contributes to the improvement of global public health.

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