

Supplies for humanitarian aid and development countries : the quality of essential multisources drugs

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Although the essential multisources drug is currently the only way of making drugs financially accessible to most of the world's population, in no case should quality be sacrificed. Yet the guarantee of a drug's quality cannot be summarized with a good manufacturing practices certificate and quality control test results. This article will discuss some of the difficulties encountered in guaranteeing the quality of pharmaceutical supplies. It will particularly emphasize risks due to the origin of raw materials. A cornerstone of health, the drug should meet three criteria : quality effectiveness and safety. Due to its complexity it requires rigorous and specific supply procedures.

Si le médicament essentiel multisources est actuellement l'unique possibilité de rendre financièrement accessible le médicament à la majorité de la population mondiale, en aucun cas cet approvisionnement ne doit se faire au détriment de la qualité. Or la garantie de qualité d'un médicament ne peut se résumer à un certificat de bonnes pratiques de fabrication et aux résultats des tests du contrôle qualité. Ce texte essaye d'aborder quelques-unes des difficultés rencontrées pour garantir la qualité de l'approvisionnement pharmaceutique en insistant particulièrement sur les risques provenant de l'origine des matières premières. Pierre angulaire de l'accession à la santé, le médicament doit répondre aux trois critères, qualité, efficacité et sécurité, et, du fait de sa complexité, nécessite des procédures d'approvisionnement rigoureuses et spécifiques.

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The idea of quality has taken on increasing importance in the supply of drugs, whether in terms of national policies in developing countries or the different medical/pharmaceutical aid programs.

However, a distinction must be made between quality of drugs and quality control. The quality of a drug encompasses everything, from its development and manufacture to its final use by the patient. Quality control is but one tool which, associated to a reference, brings a certain element of verification to certain criteria of the quality of a drug. We must then complete the evaluation methods of drugs, taking into account that WHO (World Health Organization) certification of products entering international trade has certain guarantees. We must even go further to allow developing countries to set up their own evaluation references and specifications while taking into account their own particular limitations.

Open international tenders have the advantage of favoring competition, which tends to increase the accessibility of drugs, but the principal drawback is that quality is not always a prerequisite and is based solely on quality control, which in turn may lead to a false sense of security.

I. MULTISOURCE ESSENTIAL DRUGS

1. Definition

The essential drug was defined by the WHO in the 1960s in answer to the uncertainty of supplies to developing countries :
 " Essential drugs are those that meet the needs of the majority of the health need of a population; they should be available at all times in sufficient quantity and in an appropriate pharmaceutical form .

An essential drug represents both therapeutic concept (a drug that has an optimal risk/benefit ratio i.e. it can be used under safe conditions with a moderate risk and known side effects) and is economical in terms of public health. The list of essential drugs comprises a list of 400 to 500 molecules. It is regularly reevaluated by the WHO and is a model to aid countries to identify their own priorities and make their own selection. A list of essential drugs should be able to meet the majority of health problems (80 to 90%) to treat the population under normal conditions.

This model list (the eighth [1] is currently in force) has permitted better international coordination in developing health care. However, the concept of essential drugs must be adapted to the prevailing situation. Each country should decide for itself which drug is essential. Thus, a specific list of essential drugs is then drawn on a national scale [2]. The end therapeutic and economic results are that generics are almost all available in generic or multisources form, according to the term employed.

A generic drug may be defined as a copy of an original medicinal drug where production and marketing have been made possible by the expiration granted it by patent of the intellectual property covering the active principle. The concept of copy is defined by the general texts (directive 87/21 of 22 December 1986) and by internal right, article R.5133-1 of the Public Health Code CSP [3] by the terms "speciality essentially similar", i.e. presenting :

- the same qualitative and quantitative composition of active principles,
- the same pharmaceutical form,
- if the case arises, bioequivalence with the original product, shown by means of appropriate bioequivalence studies.

Generic drugs were legally defined in France after a decree was promulgated regarding health expenditures, ratified in April by the Council of Ministers (article L. 601-6). The definition of a generic speciality of another speciality is "a speciality that has the qualitative and quantitative composition of active principles, the same pharmaceutical form and whose bioequivalence has been determined by the appropriate bio-availability studies; the different oral pharmaceutical forms for immediate release are here considered to be the same similar pharmaceutical form".

A distinction should be made between "generic" and the term "generic plus" (improved copies of existing drugs, on the dosage level, the galenic form, tolerance, etc.) and so called "me-too" drugs (drugs having the same therapeutic activities without being identical). The two latter types of drugs are not considered to be generics in the true sense of the term (copy-copy) or essentially similar and needing a complete registration file. True generics (copy-copy) use the initial file of the original molecule; those essentially similar may benefit from an improved procedure.

Decree No. 97-221 of 13 March 1997 concerning generic specialities which modifies the Public Health Code and the Social Security Code interpret these definitions more precisely.

Article R. 5143-8 states that generic specialities answering to this definition must be identified by a decision of the Director General of French Medicines Agency and added to a list presenting specialities by generic group. Each generic group consists of the reference speciality and specialities that are generic according to the meaning of article L. 601-6.

These active principle are : acebutolol (Sectral), allopurinol (Ziloric), amoxicillin (Clamoxyl group), amoxicillin (Hiconcil group), atenolol (Tenormine), cefadroxil (Oracefal), cefadrine (Kelsef), cimetidine (Tagamet), diclofenac sodium (Voltarene) dihydroergotamine (Dihydroergotamine Sandoz), diltiazem (Tildiem group), diltiazem (Diacor group), dipyridamole (Persantine), methyldopa (Aldomet), metoclopramide (Primperan), nifedepine (Adalate), propranolol (Avlocardyl), spiro-nolactone (Aldactone), sprionolactone altiazide (Aldactazine).

Article R. 5143-9 states criteria for exempting bio-availability studies, which are as follows :

- a) the file is simply a duplication of the MA dossier of the reference speciality and the pharmaceutical manufacturer; the manufacturing procedures and the origin of the active principle are the same as those of the reference speciality,
- b) either its bioavailability – taking into account its pharmaceutical form and the way it is administered – is not liable to differ from that of the reference speciality, or its active principle, especially with respect to its toxicity or specific requirements of plasma concentrations, is not likely to lead to important differences in terms of therapeutic efficacy or undesirable side effects ; in this case, the qualitative and quantitative composition of its components, controls of the raw materials, the method of preparation of the pharmaceutical form, controls of the finished product and, especially for solid oral forms, comparative dissolution tests in vitro, listed in the pharmaceutical documentation in the request file for an AMM, should show that the active principle of the speciality will be delivered, from the requisite pharmaceutical form, in the same way that it is from the pharmaceutical form of the reference speciality.

These exemptions are very restrictive, which is a guarantee of quality, but still leave the door open, especially for solid oral forms, still considered as potentially "bioinequivalent" and which may, under certain conditions connected to therapeutic risk, be exempted from bio-equivalence studies.

The European Committee of Specialities, via an explanatory note of December 1991, defined alternative pharmaceutical products that may differ in the pharmaceutical and chemical form of the active principle if these differences do not induce modifications that may cause important clinical changes. For example, chloroquine phosphate may be an alternative product to chloroquine sulfate in France.

The WHO prefers the wording "multisources drugs", which

are equivalent drugs from a pharmaceutical standpoint, but not necessarily from a therapeutic point of view. multisources drugs that are therapeutically equivalent are interchangeable. Drugs are pharmaceutically equivalent if they contain the same quantity or the same active principle(s) in the same galenic form, if they possess similar standards or comparable ones and are destined to be administered by the same route. Two drugs are therapeutically equivalent if they are pharmaceutically equivalent and appropriate results of studies (bioequivalency, clinical or *in vitro* pharmacodynamic studies) show that when administration is of the same molar dose, their efficacy and safety effects are essentially the same [4].

2. Price structure

The method of price calculation of essential multisources drugs is very different from that of a speciality. The principal difference is due to the fact that the essential multisources drug is intended for developing countries that do not engage in research and development (and the inherent costs) or marketing and advertising costs.

Since the manufacturers essential multisources drugs are often small operators who engender lower operating costs, their cost price then becomes the main factor for essential multisources drugs. The cost of raw materials may account for 50 to 65% and labour costs for 20 to 35%. Low labour costs in certain countries cannot, therefore, sufficiently explain the substantial price fluctuations.

3. Regulatory aspect

Under the aegis of the European Commission (DG VIII) and the French Ministry of Cooperation, a document entitled *Exchange of drugs between European Countries and Developing Countries* [6] gives a summary of the present state of affairs and the effectiveness of the present export regulations of drugs from seventeen European countries, and describes of the principal problems. This document also covers the regulatory status of the pharmaceutical market in nineteen developing countries.

It is a fact that countries of the European Union are the principal suppliers of drugs found in developing countries, even if the place of manufacture, in the sense of production, may often not be located in the European Union. Analysis of the situation in seventeen European countries has shown that several shortcomings exist in the export legislation of some of these European countries. The list includes :

- authorization of sale without adequate revision of old drugs,
- relatively imprecise controls regarding good manufacturing practices for exported products,
- lack of quality control, innocuity, and efficacy of products that have not previously been marketed,
- a drug that has obtained marketing authorization has not been marketed in its own country,
- authorizations granted solely for export of a product that

- give the impression that it has been completely approved,
- no special arrangements are foreseen for drugs for which marketing authorization has not been granted,
- no special arrangements have been made for drugs that have been withdrawn from the market,
- free trade zones are not properly controlled,
- information on drugs to be exported does not conform to that given for drugs authorized for their own internal market,
- there is no legal requirement for language on labels,
- existing controls are not applied.

In the developing countries reviewed, there does appear to be an improvement in pharmaceutical legislation. Thus, with one exception, all countries have undertaken to establish legislation and programs in order to control the pharmaceutical market. All locally produced or imported drugs have to be registered with the requisite authorities, except with the notable exception, in many countries, of drugs supplied by international aid organizations. However, with regards to open tenders, distributors are unable to register all the drugs that they distribute.

The WHO system of certification is not often or poorly used, except for certain international tenders. Proof of registration in the country of origin is requested. One finds a great variety of "certificates" that do not always correspond to those issued by exporting countries, nor to those recommended by the WHO.

Thus, the WHO specifies that for each drug, delivery by the exporting country [4] should include :

- a declaration regarding its registration (marketing authorization) status,
- a pharmaceutical product certificate,
- a certificate of the batch number of the pharmaceutical product.

Taking France as an example, until 1992, drugs intended for export were not registered for the in-country market, but had a "certificate of free sale" or "authorization L. 603". These documents solely certified manufacturing compliance with national regulations according to the GMP. The law of 8 December 1992 modified article L. 603 of the CSP, and by applying this decree it cancelled the said certificate. This was replaced by the following procedure (Art. R. 5142-18) :

"Drugs for export that do not have an MA must have a declaration, from the French Medicines Agency, before export; when it is a first export of this drug to an importing country, the agency must have confirmation of receipt of this document. Certificates of the opening of the firm and good manufacturing practices must accompany this declaration". For drugs that do have a marketing authorization, the Agency issues a "free sale certificate".

This legislation has been subject to much litigation [6], especially in terms of the wording of article L. 603 and the WHA 45.29 directives of 14 May 1992 of the WHO, which placed manufacturers of generics in a situation where they

cannot supply documents requested by the WHO, and which are already requested by several countries.

Article L. 603 [3] stipulates that the pharmaceutical company that exports drugs should provide a declaration to the Ministry of Health stating the reasons why this authorization is not available. The Health Minister informs the Health Minister of the importing country of the reasons. There appears to be a transfer of responsibility from the administrative authorities to the manufacturer, who assumes pharmaceutical responsibility. If the attitude of the administrative authorities is clear, in the sense that they do not evaluate these drugs, they are wrong in that they are relieving themselves from their responsibility for the quality of exports, especially towards developing countries.

II. THE PRINCIPLE OF QUALITY / SAFETY / EFFICACY

These complementary criteria are not easily dissociated and express quality, in the broad sense of the term, of drugs as foreseen by the ICH (International Convention of Harmonization) [7]. Quality depends partly upon raw materials (active principles, excipients, research on impurities) of manufacturing, packaging (stability studies) and validation of analytical procedures. Safety or innocuity is determined by studies of carcinogenesis, toxicity, pharmacokinetics and teratogenesis. Efficacy is generally revealed by clinical tests and indirectly by bioequivalence.

For essential multisources drugs, these three concepts should be specifically taken into account. At present, this is made up of a known molecule whose therapeutic activity is known so that clinical studies do not have to take place. Only bioequivalence may need to be demonstrated. Also, for a raw material with a profile listing impurities and known degradation products, safety is a parameter that may be found in the bibliography. Finally, stability studies consist of several intrinsic and extrinsic factors of the drug to which special attention should be paid. In fact, for essential multisources drugs, these three descriptions of quality, safety and efficacy are based on the concept of quality of raw materials, stability studies and bioequivalence.

1 . Quality of raw materials

Raw materials may be defined as :

- raw materials themselves, in which one should make a distinction between the active principle and the excipients,
- the accessory raw materials, manufacturing intermediaries (fluid dispersing agents, propellants), primary packaging articles.

1.1. The active principle

This is the focal point of the drug. For a generic drug, it takes on even greater importance. Most essential drugs are available in generic form, which in turn implies that they are

in the public domain. Raw materials are equality multisources but not necessarily interchangeable. It is important to note that available in generic form, which in turn implies that they are the cost of a raw material may vary greatly. This is due to different parameters :

- labour costs,
- the size and commercial strategy of the company,
- quality and especially purity.

This last parameter is very important for public health. It is the one element where we can exert a positive influence. However, it is difficult to show that a raw material that complies with a test of the European Pharmacopoeia may not necessarily be of good quality, as we shall try to explain in this chapter.

In addition, it is important to know that the price of the raw material is often more than 50% of the industrial cost price, which may lead manufacturers of generic drugs responding to tenders to try and economize on the purchase price of raw materials.

The quality of the raw material is unfortunately one of the parameters that are rarely taken into account in granting export permits for exporting generics that do not have an MA certificate in European countries, and this parameter is often not even considered as important by various purchasers. Take, for example, a drug that has an MA in France. The manufacturer must produce a certain number of guarantees :

- a declaration in the MA file of the name of the supplier of the active principle and also of a substitute supplier; notification must be made of any changes and equivalence must be proven,
- manufacturing procedures of the active principle must be noted in the MA file, stating the impurities, the related substances and the degradation products which will then be noted in the closed portion of the DMF (Drug Master File) [8] submitted to the Health Ministry ; in addition, the starting products and those added in the synthesis have to be part of the monography,
- evidence is to be shown of the applicability of the pharmacopoeia tests to the impurities, related substances, degradation products of the active principle ; by definition, in research one only finds that for which one is looking for; indeed, pharmacopoeia monographs (impurities, related substances and degradation products) are based on the latest synthesis procedures, but do not show other catalysers, ingredients, precursors, solvents or degradation products resulting from other methods of synthesis which be potentially toxic,
- specifications relating to the active principle that may affect the pharmaceutical and therapeutic quality of the finished product are not necessarily described in a pharmacopoeia (granulometry, crystalline form, polymorphism, etc.).
- standard stability studies, experimental or bibliographical should be detailed in the file ; if the synthesis procedure is recent, the active principle should be submitted to stringent tests to bring out the degradation products,
- if the method of synthesis produces related substances or unknown degradation products, their innocuity or their limit level in the active principle must be shown.

Simply changing the supplier of the active principle brings all these parameters to the fore once again.

Figure 1 emphasizes the importance of the method of synthesis in drug quality. This diagram illustrates the great importance of quality in the drug. In addition since the monographs in pharmacopoeias are based on the latest synthesis procedures, with impurities, related substances and degradation products all well defined, a different type of synthesis should be the subject of an adapted control, something that is not always done. The monographs in the third edition of the European Pharmacopoeia now specify what related substances are brought out in the tests.

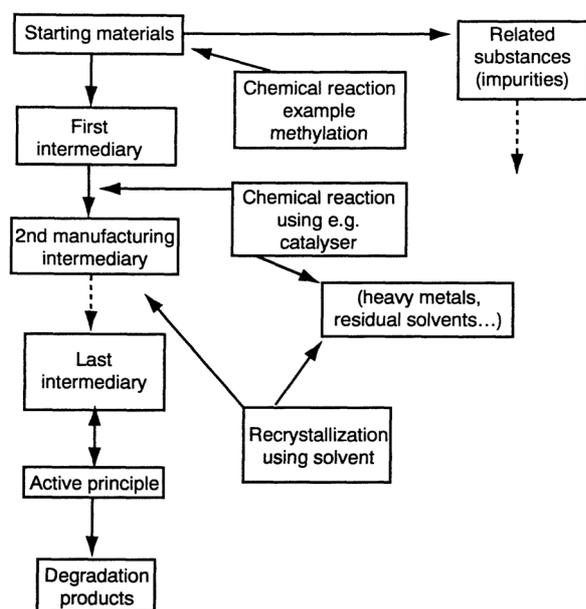


Figure 1 - Stages of drug synthesis.

Should the purchaser of generic drugs desire to conduct analyses, relying solely on the monographs of a pharmacopoeia may give him a false sense of security, with questionable results that may affect health due to the risk of toxicity of related substances and degradation products as well as impurities if the synthesis method is different.

1.1.1. Supply sources of active principles

The market for the raw material, the active principle, is now worldwide and is particularly concentrated in Asia. Certain products are at present only manufactured in Asia. There is no question of denigrating the quality of Asian manufacturers, but rather to explain problems of quality which may be encountered :

- it is difficult to know the actual suppliers when they are located such a great geographical distance away [9] ; in addition, Asian manufacturers of raw materials have little export experience and often deal with commercial companies, which tend to break the bond between supplier-client relationships ; a commercial company may deal with several manufacturers for a similar product,
- even when the true manufacturer is known, problems may

- also arise for the supplier audit due to distances involved,
- the manufacturer of the raw material should make known his synthesis procedure to ensure that the generics manufacturer shows concordance between pharmacopoeial tests and the profile of impurities and degradation products of the raw material, it is not very reassuring when auditing a supplier one barely knows,
- for various reasons, there may be delivery delays, which in turn may lead the manufacturer of generics to change suppliers if, for example, he must meet a deadline or if the intermediary supplier of raw materials has altered his supply source.

These four potential problems show how suppliers situated at great distances need greater vigilance to ensure quality. However, some countries have very good suppliers of raw materials of very high quality backed up by a precise documentary system and tests that meet pharmacopoeia standards. Then the price factor enters the picture and becomes the determining factor in accessibility of drugs.

1.1.1.2. Important parameters in the quality of raw materials

1.1.1.2.1. Physical characteristics of a raw material that impact on the bioavailability of the finished product

Polymorphism and pseudo-polymorphism

Polymorphism may be defined as the capacity of substances to exist in the solid state under different crystalline or amorphous forms. The name pseudo-polymorphism is given, by analogy, to the solvate or hydrated forms of the molecule [10]. It has been clearly demonstrated that a correlation exists between the polymorphism of the active principle and the bioavailability of the finished product. Examples of studies of these correlations are presented in table I.

Table I. Examples of correlation between polymorphism of active principle and bioavailability of finished products [10].

Active principle	Type of measurement of bioavailability
Ampicillin	Different plasma levels for anhydrous and trihydrate forms in suspension
Aspirin	Subcutaneous implantation, plasma levels
Carbamazepine	Similar plasma levels in human for anhydrous and trihydrate forms
Cimetidine	Plasma levels in rats
Griseofulvine	Plasma levels in dogs
Hydrocortisone acetate	Percutaneous absorption
Insulin	Amorphous and crystalline
Mebendazole	Acute toxicity and activity in mouse
Methylprednisolone	Identical pellets for two forms implanted in rat
Chloramphenicol palmitate	No therapeutic effect in some commercial forms
Plentobarbital	Plasma levels in rabbit

Toxic effects may also be linked to polymorphism (e.g. mebendazole). Polymorphism may be transformed with the influence of different parameters or events, such as being put into solution, or following mechanical effects, such as crushing or compression. Climatic conditions such as storage may also have an influence.

Size of particles [10]

This parameter influences bioavailability only in the case where speed of dissolution is slower than the constant of resorption. This occurs with griseofulvine, digoxin, tetracycline, tolbutamide, norfloxacin.

A note should be made that this parameter is often associated with polymorphism. Finally, not only particle size, but also their distribution, have an effect on their manufacture, especially when compressed.

Morphology of the crystal [10]

Flaws in the crystal as well as the crystalline surface may give different speeds of dissolution (aspirin, paracetamol, acetaminophen, nitrofurantoin).

1.1.2.2. Characteristics of raw materials that have an effect on toxicity

The toxicity of raw materials [11] may be due to related substances (appearing during synthesis), to degradation products (appearing after synthesis) and to impurities and residual solvents appearing during synthesis.

Related substances

These appear during synthesis of the active principle, and should be identified and qualified on the toxicological level. They may consist of starting products and their impurities, products of secondary reactions of isomerization.

Residual solvents

These are used for recrystallization of the product and are divided into several classes :

- class 1, toxic to be avoided : benzene, dichloroethane, trichloroethane, carbon tetrachloride, etc.,
- class 2, toxic but acceptable : acetonitrile, chloroform, cyclohexane, toluene, pyridine, methanol, dioxan, dimethyl formamide, etc.,
- class 3, the others : ethanol or other solvents that have little toxicological data (ether).

For each class, there is a European standard for research methods and on their limits.

Heavy metals

They appear during synthesis either as a catalyser or from

manufacturing equipment. They are intrinsically toxic and, even in tiny amounts, they may cause catalytic reactions of degradation of the finished product that may lead to eventual inactivation or toxicity.

Degradation products

They appear during storage under certain types of conditions, and may also be responsible for toxic phenomena, such as, for example, epimerization of tetracycline into anhydro-4-epitetracycline under the effect of heat and humidity, and is responsible for renal tubular lesions of the Toni-Debre-Franconi type.

1.1.2.3. Characteristics of raw materials (basic products) that affect their pharmacotechnical qualities

These pharmacotechnical qualities do not have direct repercussions on the toxicity of finished products but may have some secondary effects on their stability and bioavailability. These characteristics are easier to define and bring under control. Some characteristics are, for example [12] :

- measurement of particle size distribution,
- measurement of aptitude to compress,
- specific surface analysis,
- measurement of the flow index by resistance to shear.

The analysis of these parameters helps show to what point the quality of the active principle has the greater prevalence in the quality of the finished product, and that simple conformity with any pharmacopoeia is insufficient to prove the quality of a raw material [13].

It is important to note that, for economic reasons due to competition, the supply of active principle from multisources brings into play each time all the parameters which are rarely taken into account in the selection of drugs found at the international level when tenders are called.

1.1.3. Quality guarantees

1.1.3.1. The Drug Master File (DMF)

For a marketing authorization, European Union legislation requires that the regulating authorities be supplied with detailed documentation on the drug.

In order to maintain the know-how of the manufacturer, certain member countries have instituted a confidentiality procedure which permits producers to directly register the requisite information with authorities as a reference file (DMF or Drug Master File) [8]. When registering a pharmaceutical speciality, the manufacturer of the drug can deposit information regarding his industrial expertise directly with the registration authorities. This documentation will be examined by an accredited consultant when the request is made for an MA for this speciality, under conditions that safeguard confidentiality. In addition, the manufacturer of the drug supplies whoever requests

an MA sufficient information to allow him to have control over the pharmaceutical quality. Introduction of the DMF system in Europe is the result of the need to reconcile two divergent attitudes :

- that of registration authorities, who request detailed documentation on the manufacture of drugs,
- those of the chemical and pharmaceutical industries, which seek to safeguard their expertise and abilities. This DMF procedure is recent, for it was established in France in July 1990, but it has existed in the United States since 1970.

1.1.3.2. Procedure of certification conforming to the European Pharmacopoeia

This procedure, recognized by all member States, is to permit the producer of a raw material for pharmaceutical use to furnish proof that the purity of a substance is adequately controlled by the monograph of the European Pharmacopoeia. It is possible that impurities that come from certain synthesis procedures are not ascertained by the monograph of the Pharmacopoeia. The pertinence of the monograph may then be shown by one of the four following methods, in which the drug manufacturer may submit :

- . documentation to the commission of the European Pharmacopoeia, the object of which is to evaluate whether the product is appropriately controlled according to the monograph for the method of manufacture used,
- . any other evaluation proof,
- . a detailed description of manufacture,
- . a European drug reference file.

This concerns all drugs registered in the European Pharmacopoeia and, in the short term, it tends to replace the DMF. The list of raw materials and suppliers is available [14].

All these regulatory, scientific and technical aspects make up a large part of the cost of the drug, which itself represents approximately 50% of the industrial cost of the finished medicinal product. In order to " get " a part of this market, there is a great tendency to be permissive and remiss in one of these parameters, especially when the quality aspect of the raw material is often not taken into account when opening a tender

1.2. Excipients

1.2.1. Definitions and parameters

For a long time, excipients and adjuvants were considered inert. However, the same requirements and limitations as those that apply to the drug must be taken into account, even more so, since excipients often make up the bulk of a formulation. In addition, the great diversity of excipients [15] and use of excipients in other industries makes it even more difficult to establish standardized quality. The chemical quality, the purity of crystals, and technological quality must all be considered. A rheological study of different powders should be carried out, along with tests for solubility and kinetics of dissolution, determination of specific surface, establishment of a

granulometric curve, and shredding. Any change in the excipient may cause variations in bioavailability and produce toxic phenomena or allergies.

Several examples have been described. One of the most serious is the paracetamol (acetaminophen) syrup found in Haiti that caused several deaths. The level of diethylene glycol, a toxic agent, was very high in the glycerin incorporated into the syrup as an excipient. The detection of diethylene glycol is not foreseen in the glycerol monographs in different pharmacopoeias. Tests for functional activity help define and control the physical characteristics of excipients.

1.2.2. Quality guarantee

1.2.1.1. IPEC

The IPEC (International Pharmaceutical Excipient Council) is an association created in 1992 consisting of worldwide manufacturers and users of excipients. Its aim is to harmonize the use and quality of excipients throughout the world. This association published the *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients* in 1995.

1.2.1.2. EEDMF

This certification procedure currently under development is similar to the DMF but applies to excipients.

1.3. Containers

1.3.1. Definitions

The container for pharmaceutical use is an article that contains or is intended to contain a pharmaceutical product and which is, or may come, in direct contact with it. The closure forms part of the container (European Pharmacopoeia third edition).

1.3.2. Eventual problems

Generally, glass possesses a certain measure of safety, for it is inert, although in an alkaline medium degradation takes place in the vitreous lattice. On the other hand, plastic containers may be inconvenient due to container/content interactions, often seen with liquids. In addition, the high rate of humidity in tropical countries is may cause interactions between powders and container walls.

There are two types of interactions :

- migration and adhesion of contents of plastic materials by the mechanism of adsorption, thus modifying the stability of the product and eventually causing changes in the plastic material,
- a shift of the constituents of the contents towards the sides of the container, thus modifying the stability of the pharmaceutical preparation and possibly causing intolerance reactions or toxic phenomena.

A well-known example is that of polyvinyl chloride, which may cause migration of adjuvants (antioxidants, stabilizers, plastifiers, strengthening agents, colouring agents, inert particles, etc.)

1.3.3. Quality guarantees

1.3.3.2. Intrinsic control of containers

The monographs in the European Pharmacopoeia outline the tests required for quality control of containers. This step of quality control must be accompanied by an compulsory audit, for we must always remember that the supplier of the container does not necessarily know the quality requirements of the pharmaceutical industry. The manufacturer of drugs must clearly define his detailed specifications in writing. For example, polymers should be identified mostly by infrared. Additives and adjuvants are considered to be analogous substances and on this basis have limits of content [15].

1.3.3.3. Container/contents interaction

This test, relatively expensive, is used to demonstrate that there is no interaction between the container and the finished product from the time of manufacture and during the stability study.

2. Stability studies

The stability of a drug may be defined as its ability to maintain its chemical, physical, microbiological and biopharmaceutical properties within specified limits during the entire extent of its validity [4]. Since the active principles of essential generic drugs are known molecules (degradation mechanism and stability of the active principle), in most cases it is possible to limit stability studies of the finished product. The stability of pharmaceutical preparations depends on extrinsic (temperature, humidity and light) and intrinsic parameters. Among the latter, a distinction should be made between factors related to raw materials and pharmaceutical form and packaging. There are two types of stability studies[4]:

- accelerated degradation studies, meant to increase the speed of physical or chemical degradation of a drug by subjecting it to extreme storage conditions during an official study program of stability studies,
 - stability studies in real time : experimental study of the chemical, physical, biological and microbiological characteristics of a drug during its period of validity and foreseen use and beyond, in storage conditions encountered on the market for which it is intended.
- For stability studies requirements, the world can be divided into four climatic areas [4] :
- area I : temperate climate,
 - area II : subtropical climate with possibility of high humidity,
 - area III : hot and dry climate,
 - area IV : hot and humid climate.

The average climatic conditions encountered in these zones, along with storage conditions obtained from stability studies in real time, are presented in *table II* [4].

Table II . Mean climatic conditions and storage conditions [4].

Climatic area	Values measured in open air		Values measured in warehouse		Storage conditions for real time studies	
	°C	% HR	°C	% HR	°C	% HR
I	10,9	75	18,7	45	21	45
II	17,0	70	21,1	52	25	60
III	24,4	39	26,0	54	30	35
IV	26,5	77	28,4	70	30	70

Area I applies to few countries ; it is therefore suggested to manufacturers who wish to market their products in temperate climates to undertake stability studies of area II, which corresponds to temperature and humidity conditions specified by the ICH. However, for those manufacturers interested in the world market, it is recommended that they use stability studies of parameters in area IV.

European manufacturers of drugs are not specifically required to meet the specifications of area IV for stability studies for marketing in Europe or for export authorization. Practical experience confirms this, since most of the quality problems found in situ are essentially problems of stability and not problems linked to the intrinsic quality of the product, as evidenced by inspection of the finished product by the importer. Quality control on reception cannot identify a stability problem, for this can only be quantified after examination of the manufacturer's file. An important change in stability is defined as:

- a 5% decrease in the strength of the active principle compared to the initial strength, resulting in sub-dosage and leading to resistance in the case of antibiotic treatment,
- the presence of any degradation product specified in a higher amount compared to specifications (toxic risk or inactivation),
- pH not within specified values,
- speed of dissolution of twelve tablets or capsules lower than specified limits, leading to an eventual loss of bioavailability,
- specifications regarding appearance and physical properties not present.

Tests for relative high humidity conditions are very important, because the risk of degradation of semipermeable packaging is much higher. Stability studies are one of the most important parameters to be considered for supplies of drugs for three principal reasons :

- climatic conditions in developing countries are very different from those of European countries, which serve as a basis for references for studies,
- poor stability results are serious, because drugs may become toxic or inactive,

- stability cannot be evaluated by quality control of the delivered finished product.

3. Bioequivalence

Bioequivalence is the third criterion for quality in the broader sense of the term but, according to ICH recommendations, it is indirectly related to the concept of efficacy. The definition of bioavailability is "the speed and absorption by the body, from a pharmaceutical form, of the active principle or its therapeutic fraction intended to become available at the sites of action" and that of bioequivalence : "the equivalence of bioavailability".

On the whole, bioavailability of an active principle depends on intrinsic (granulometry, solubility, speed of dissolution, degree of purity, etc.) and extrinsic factors (manufacturing adjuvants, manufacturing conditions and preservation, packaging of the finished product), without taking into account interindividual variations [16].

To recapitulate the terms used by the WHO, a multisources (generic) drug must be interchangeable, thus clinically equivalent to a reference drug [4]. Finally, for drugs to be pharmaceutically equivalent, in order that they should be considered as interchangeable, it must be proven that they are equivalent from a therapeutic point of view. Different methods may be suggested [4] :

- comparative bioavailability studies (bioequivalence) in man consist of titrating the active principle or one or several of its metabolites in an accessible biological liquid such as plasma, blood or urine,
- comparative pharmacodynamic studies in humans,
- comparative clinical trials,
- dissolution tests *in vitro*.

The WHO has also established criteria that exempting from equivalence trials. This primarily concerns drugs for parenteral use (IV, IM, SC, etc.), drugs in solution for oral administration, drugs in powder form that are to be reconstituted into solution, medical gases as well as drugs for auricular, ophthalmic, topical use, or for inhalation and pulverization. There remain, then, different pharmaceutical forms for which equivalence must be demonstrated and, as for essential multisources drugs, tablets and capsules are the most frequent subjects of discussion and/or interpretation. It is evident that for these pharmaceutical forms, bioequivalence studies are best to prove equivalence and thus the criterion for efficacy. Unfortunately, this study is not always conducted for essential multisources drugs in open tenders due to three interconnected reasons :

- this type of study is very expensive in France and in Europe and significantly increases the cost of a drug,
- the raw materials market does not easily allow for a steady supply source and, due to the impact of the quality of raw materials on bioavailability, manufacturers hesitate to initiate such costly tests,
- there is no clear definition for which drugs in this type of

study may be replaced by a dissolution study *in vitro*.

The WHO stipulates that *in vitro* dissolution studies may be useful to show the equivalence of two multisources drugs, but it is recommended that it be used as little as possible and especially not as the sole proof for tablets and capsules, since the dissolution test is principally applied to these two pharmaceutical forms. On the other hand, if dissolution of the product to be evaluated and the reference product is rapid enough (> 80% in 15 min), their *in vivo* equivalence may be presumed.

However, article R. 5143-8 allows for the possibility to conduct dissolution kinetics *in vitro* to demonstrate bioequivalence. Much work has been done in the field of *in vivo/m vitro* correlations.

A report of the SFSTP commission [17] shows the biopharmaceutical relevance of *in vitro* dissolution trials of pharmaceutical forms, especially conventional per os within the framework of the strategic development of these forms and control of industrial lots. This work shows that for a conventional solid pharmaceutical form for oral use, the speed of dissolution of the active principle at a minimum of 80% in 30 min in a standard medium (distilled water or aqueous buffer) allows us to be reasonably certain that there will be no bioavailability problem linked to the dissolution kinetics, this not limiting it. We thus obtain a predictive value without prejudging the *in vitro/m vivo* correlations which have more limited applications and necessitate supplementary validation.

Four types of *in vitro/m vivo* correlations have been defined by other authors [18] :

- level A : relationship 11 between *in vivo* speed of dissolution and *in vitro* speed of dissolution (mathematical equations which describe the one describe the other),
- level B : correlation by statistical methods,
- level C : relationship from point to point,
- level D : the least worthy (disintegration performance *in vivo*).

Correlation at level A is applicable mostly to slow-release formulations. For other oral pharmaceutical forms where these release-dissolution parameters do not play any role in absorption (especially if they are less than 30 min), these correlation's are less important.

The EC guidelines on bioequivalence testing [19] list the criteria that evaluate the need for bioequivalence studies *in vivo*. For oral formulations for immediate release, six criteria for eligibility studies of bioequivalence exist. These criteria apply, among others, to drugs with a narrow therapeutic range or complex pharmacokinetics (absorption < 70%, window of absorption, non-linear kinetics, presystemic elimination > 70%) or even unfavourable physicochemical properties (weak solubility, metastable modifications, instability, etc.) and documented bioavailability problems.

If none of these criteria apply to the drug, an *in vitro* dissolution test may suffice to show bioequivalence. However, it is difficult to apply this test to several generic drugs. It would be preferable, as has been done in some countries, to create lists of products that do not require bioequivalence studies in accordance with therapeutic risks.

It would be a judicious choice to test dissolution kinetics of the drug to be tested and of the reference instead of respecting a threshold value in a given time and in several media, carefully selected in relation to the profile of the product. It is true that for drugs with a narrow therapeutic range that present undesirable and/or therapeutic effects depending on the quantities of active principle delivered within a certain period of time to the body or presenting delicate or variable pharmacokinetics, it becomes necessary to conduct bioequivalence studies; this is, however, not always done due to the cost factor.

III. MEANS AVAILABLE TO DEVELOPING COUNTRIES TO EVALUATE DRUGS

At present, developing countries are increasingly perplexed regarding their supplies for essential drugs. Central purchasing depots have been created at the national level and operate according to the principle of open tenders. However, if this principle allows drugs to be obtained at a very low price, it has the drawback of insufficiently emphasizing the concept of drug quality, especially in an international context that is not uniformly regulated.

Before presenting the means available to developing countries to evaluate multisources drugs, it would be convenient to list the shortcomings and the specifics of this particular market :

- essential drugs are often constituted of older molecules and consequently files that have been drawn up before modern data came into play,
- all countries in the world may reply to open tenders,
- a great proportion of drugs found in these open bids do not have an MA (an official certificate of authorization) in their country of origin, not necessarily because these drugs are of inferior quality, but because the manufacturers produce mostly for export and do not have a local marketing strategy for their products; furthermore, a product may have an MA in its country of origin for a given packaging (blister pack of twelve capsules, for example), whereas packaging used in developing countries or in humanitarian aid programs come in boxes of 500 to 1000 capsules, quantities for which there is no MA certificate ; the same problem exists for drugs marketed under a speciality trade name and do not have an MA for sale in INN;
- if some products do have an MA in their country of origin, these are not all equivalent from one country to the other on a technical or economic basis, even within the community,
- export certification from Europe does not meet uniform and safety procedures for the importer,
- the majority of developing countries do not have test

laboratories for drugs,

- a problem also exists in importing countries that do have an MA in the sense that the procedure is not standard in all developing countries and criteria are not always sufficiently selective ; the great distances involved do not always permit adequate verification between the file and the actual practices of the manufacturer.

Means available to developing countries for evaluation of drugs are as follows :

- quality control of the drug,
- audit of the manufacturer,
- registration of the drug in the country of manufacture and in the importing country.

Each of these three approaches has its advantages and disadvantages, but their association brings on a combined action that is difficult to separate. It should be noted that, for drugs marketed in Europe that have an MA, the evaluation system works very well by using the above-mentioned three approaches.

If for example in France – and it exists in other European countries as well – the MA is granted by the Drugs Agency after evaluation of the manufacturer file. Analyses are carried out both by the Directorate of Laboratories and Controls at the time of registration and also after samples are taken when inspecting the manufacturer. Inspection ensures compliance with GMP, but also complies with the batch record to the reference which in turn is the MA file.

If, on the other hand, the product does not have an MA, the Drug(s) Agency ensures GMP norms are attained via inspections and quality control. However, conformity of the batch record with the reference is not inspected, because no official reference file exists as an MA file. These two cases are illustrated in *figure 2*. As already explained a previous section, drugs without an MA manufactured in Europe are not sufficiently evaluated, and it is up to the importer to draw up his own rules, a difficult task for a number of developing countries.

Tins presupposes that buyers in developing countries must adopt a practical program that includes the three steps of quality control, manufacturer audit and preference for a product registered in its country of origin or in the developing country in question, with a study of type of registration which has not already been harmonized in Europe, while taking into account the price, which allows for accessibility to care services.

1. Importance and limits of quality control

1.1. Importance

1.1.1. Obligations of the manufacturer/supplier

Quality control offers important advantages in cases of open tenders. It allows, in the written submission of the tender,

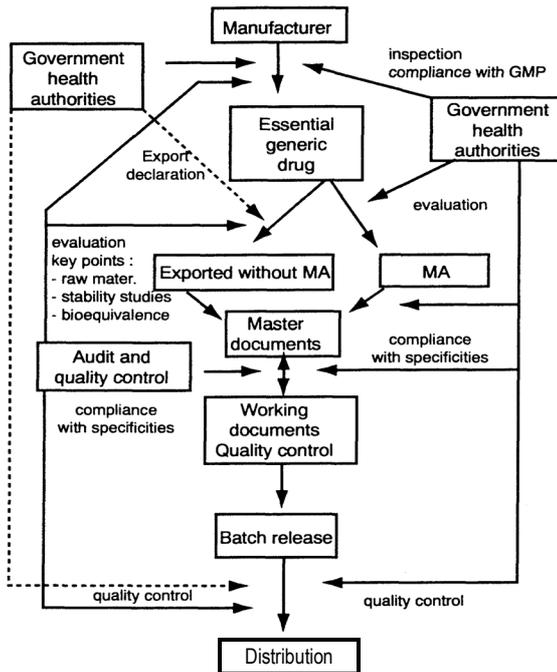


Figure 2 : Evaluation of the quality of essential generic drugs.

to link the conditions for payment to acceptance of batches and to eliminate disreputable manufacturers. However, it is necessary for the analyst to understand analytical methods and manufacturer reference standards in order to remove any ambiguity in interpreting results. It is important to remember that quality control is not an end in itself and it may, if used by itself, lead to a false sense of security and irrational rejection of drugs by using inappropriate analytical methods.

1.1.2. Interesting indicators by selected markers

It is preferable to use well-established markers for drugs. For example, the dissolution test should be used systematically for drugs that generally have dissolution problems [20]. In addition, titration of degradation products is very important in the case of tetracycline, the titration of active substances is recommended for antibiotics and products with a narrow therapeutic range. For large quantities of solution, the search for endotoxins, the cause of pyrogens, will give better information than a test for sterility, which has little chance of being positive.

1.1.3. Verification of similarity between the manufacturer's file and the quality of the product

In association with the manufacturer's file, quality control is one of the methods to ensure conformity of the product with the manufacturer's reference.

1.2. Limits

Limits of pharmacopoeias

Pharmacopoeias were not published with a view to making quality control of drugs listed in international tenders. The European and French Pharmacopoeias list control methods for

raw materials, and not finished products. Only the International Pharmacopoeia, not yet completed, the United States Pharmacopoeia (USP) and the British Pharmacopoeia (BP) describe analytical methods for finished products, but they are not always applicable, because the excipients used may lead to a loss of specificity. Monographs of finished products do not contain all the dissolution tests, and when they do exist, they are not always selective.

1.2.2. Very often there is a lack of reference for a final product for external controls

Methods of titration for finished products of drugs are understood to have been updated and validated by the manufacturer using criteria as defined by Good Laboratory Practices and the ICH. The external analysis of the drug undergoing quality control should, in theory, have this analytical reference to avoid erroneous results due to lack of specificity, precision or exactness of the titration method.

1.2.3. Quality of the raw material not evaluated by control of the finished product

Quality cannot be evaluated by control of the finished product, with the exception of certain powders for injectable suspensions. In fact, knowledge of the synthesis procedure is of considerable importance in verifying the quality of the active principle. Furthermore, since monographs in pharmacopoeias are based on the latest synthesis processes containing impurities, analogous products and well-defined degradation products, a different type of synthesis should be the subject of an adapted control, which is not always the case.

Reference to a pharmacopoeia may, in this case, lead to a false sense of security, with harmful results for public health, given the potential toxicity of analogous substances and well-defined degradation products and impurities. The third edition of the European Pharmacopoeia lists, at the end of its monographs, the impurities and analogous substances found in the tests. Quality control of the drug must always be attached to a specific system of documentation (DMF, certification of the European Pharmacopoeia) or an undertaking of the manufacturer ensuring compliance between pharmacopoeial test and quality of the active principle.

1.2.4. Quantifiable stability on file or "too late" to return to field

Analysis of a drug carried out at time T1, on receipt of a delivery, may be satisfactory, but its stability may be "deficient", especially under difficult storage conditions, which leads to a loss of activity before the expiry date [21]. This type of problem may arise when the active principle is unknown when bought from a casual or infrequent supplier. Stability studies of the active principle and of the finished product, whether from experiments or bibliographical, should be recorded in a file.

In addition, container/content interactions, aggravated by storage in tropical conditions, can only be evaluated by a file.

1.2.5. Microbiological control can give a false sense of safety : conception of parametric release

All quality control of the finished drug product may give rise to errors of interpretation, especially in the case of samples taken to represent batches from a large lot. The manufacturer should define a procedure for taking samples based on validation and size of the manufactured lot. These elements are not necessarily known by the external analyst, and it is all the more important in the case of microbiological controls of injectable preparations.

A side from sterilization, the sterility of an injectable drug is guaranteed :

- by a controlled atmosphere in the filling and packaging areas,
- by validation of production and sterilization operations.

However, the test for sterility is the only analytical method for quality control of products. This phenomenon contradicts the desire to evaluate conformity with sterility according to production parameters and validation of the procedure (parametric release of the batch) [22].

1.2.6. Difficulty of testing for pyrogens/validation problem with LAL

The test for finding pyrogens as described in the pharmacopoeia was done on the rabbit. Difference in temperature before and after administration of the injectable drug was the determining parameter for presence or absence of pyrogens. This requires having an animal laboratory which entails all types of regulatory and structural constraints. A proposed alternative is the search for endotoxins on cells (LAL), but this promising method has limitations :

- need to validate each procedure on for new drug problems arising from iack of a reference product from the manufacturer,
- lack of correlation between the LAL test and research on the rabbit for several products.

The European Pharmacopoeia has only one monograph (water) recommended for the LAL test for detecting pyrogens. To summarize the principal limits of quality control, "quality is not controlled, it is manufactured".

2. Importance and limits of auditing a manufacturer

The audit of a manufacturer has different objectives, according to the regulatory environment of the drug and the manufacturer. If the drug has an MA in its country of origin, which itself has high standards of evaluation and inspection, an audit of the manufacturer is less important and should be differently organized than one that does not have an MA in its country of origin.

Normally, within the framework of reference of the type GMP/ISO, the audit is carried out once the contract has been agreed upon. A provision to that effect should be specified in the contracts (chapter 7 of the GMP); this will ensure that the supplier's quality standards attain the confidence level required to manufacture products in conformity with the samples given. This step is more difficult to accomplish in trying to select suppliers when soliciting for international tenders. It is then preferable to audit a supplier before selection and obtain information both about the manufacturer and the drug if the supplier does not have MA certification in his country of origin. The objectives of the audit will be based on ISO/GMP references, a contributing factor in the selection of manufacturers and drugs. Several articles [23, 24] discuss ISO/GMP reference procedures, but these are only valid in the contract of an exchange representing the same organization.

At this stage it is important to present the concept of pharmaceutical establishment and pharmaceutical responsibility as follows: in article 22, Directive 75/319/CEE defines the responsibilities of the qualified person (in France this is obligatorily the pharmacist) who assumes responsibility for manufacturing, release and recall of drugs. According to the GMP, the definition of the manufacturer is "a person entitled to have an authorization to manufacture as mentioned in article L. 598 of the Public Health Code". Article L. 598 of the Public Health Code stipulates that "the opening of a pharmaceutical establishment is subject to an authorization issued by the French Medicines Agency when it concerns a pharmaceutical establishment that undertakes to manufacture, market or import drugs".

According to the GMP, manufacturing is understood to be "all operations regarding the purchase of raw materials, articles of packaging, production, quality control, release of batches as well as allied controls" and production "all operations concerning preparation of a drug, from receipt of raw materials and packaging articles, through processing and packaging until the finished product is obtained".

According to the Public Health Code (article R. 5143), labeling consists of, among others, the name and address of the

company handling the drug or product and, if it does not manufacture the product or drug, the name and address of the manufacturer.

In France, labels may at present only mention the operator of the company who is considered to be the manufacturer, but this will be changed in the near future. The above stipulations have been adopted as an exchange between countries that have the same type of rules and regulations and allow for the definition of responsibilities for the circulation of products, i.e. the supply agreement [25, 26] signed by each legal entity among and between the different groups.

However, if drugs are sent to developing countries, this regulation has not been adopted, because for the reference drug, the MA file often does not exist and limits the functions of the head pharmacist. However, these very codified procedures adapted to the "western world" allow less scrupulous manufacturers to deceive and manipulate the concept of manufacturer, manufacturing and release of batches and thus mislead developing nations. Furthermore, pharmaceutical responsibility is underpinned by a system of inspection that is meant to guarantee that it be respected.

It is to be hoped that the European countries represented by their administrative authorities extend responsibility to all drugs manufactured on the continent. It is only by this condition that the manufacturer's responsibility will be achieved.

2.1. Importance of the manufacturer audit

2.1.1. Direct contact with suppliers

An audit of the manufacturer is the sole means of verifying a contractual client/supplier relationship, in the sense of the ISO's meaning of the term, and to ensure that the conditions of sale have adhered to the schedule of conditions. The audit may also be one of the first steps of a consent agreement between drug/supplier, in the case where a drug does not have an MA.

2.1.2. Compliance with the GMP

Only an audit of the manufacturer can supply all the information on the quality systems of a firm. During the course of the audit, the following items, that have an important impact on the quality of drugs, are dealt with [27]:

- organization flow chart and definition of functions, especially of qualified personnel, those in charge of quality control and quality guarantees,
- training of personnel, hygiene,
- organization of premises, regarding flow (circulation) of people and materials,
- operational procedures and directives,
- documentary system and especially batch records,
- purchase of raw materials,
- prevention of cross-contamination environment (temperature, humidity, ventilation, controlled atmosphere),

- validation of processing operations,
- release and tracing of batches.

Administrative authorities currently grant GMP certificates without ensuring whether there is proper quality of the documentary system for products without an MA designated for export. Furthermore, a GMP certificate can only relate to partial activities : advertising, information, pharmacovigilance and follow-up of batch recall, thus creating confusion between the actual manufacturer and the distributor of Ms brand.

2.1.3. Concordance of drug with the reference product

The GMP certificate does not, at present, prove concordance of the drug with the reference of the manufacturer when the latter has not consigned an MA in the country of origin. It is most important when the manufacturer registers a drug in a country where this concordance is evaluated by an audit, because it is difficult to rely on the administrative authorities of the country of origin.

The examination must verify both the manufacturing in general as well as the products (stability studies, sources of supply for raw materials, etc.) in order to show concordance between the registration file of the drug and the actual practices of the manufacturer.

2.2. Limits

2.2.1. Time, training, cost

Due to the large number of manufacturers replying to international tenders, systematic and repeated audits cause very important time restraints. Furthermore, it may be simple for a manufacturer to conceal his weak points during an audit and thus deceive the auditor if the latter is not properly trained in the requisite techniques. Finally, the cost factor must be taken into account.

2.2.2. Geographic distances between client and supplier

This factor does not build confidence in client/supplier relations.

2.2.3. Routine examination

To be effective, an audit should not be a routine examination, but a dynamic and evolving process. A report must be made after each audit and corrections should be subject to evaluation at any time. In addition, any noncompliance detected by the client should immediately lead to an audit of the supplier, which is difficult due to the obstacles previously mentioned.

3. Importance and limits of registration of multisources drugs

A distinction must be made between the country of manufacture and the importing country, both of whom have many points in common. There is a common interest in both types of registration.

3.1. Importance

3.1.1. Stability data

Stability studies carried out according to ICH3 recommendations (in real and accelerated time) can only be evaluated with a file containing a manufacturer audit.

3.1.2. Data on analytical methods

These data are most important to carry out controls on receipt (validation problem).

3.1.3. Data on raw materials

The administrative authorities of a country thus have the manufacturing procedures of the active principle, the agreement of the manufacturer and can rationally evaluate drugs by taking into account the parameter of raw materials. It should be noted that quality control only allows for titrating and identifying that for which one is looking for. Raw materials are major public health and cost factors (on average, a raw material may represent more than 50% of the industrial cost of a generic drug). *in vivo* data studies, efficacy and data studies must be evaluated by a bibliographic file of the drug.

3.2. Limits

3.2.1. Absence of a common reference to the developing countries

The developing countries should together agree upon the contents of a registration file, thus allowing shared registration for several countries in a given geographical zone, which in turn would have the advantage of lessening administrative and financial restrictions on manufacturers, who would then be able to concentrate on the concept of quality since, once again, the price factor is the most important in international tenders.

3.2.2. The current market for generics for developing countries or humanitarian organizations operates most of the time with multisources raw materials

This diversity creates a problem in calls for international tenders, because quality parameters for raw materials are not sufficiently emphasized in the selection criteria.

3.2.3. Stability and *in vivo* studies consequently cannot be used

These studies depend on the quality of the raw material. Any change brings the reliability of these studies into question.

3.2.4. Lack of inspection to ensure conformity with references to file

The " rich " countries have agreed to mutual recognition of inspections via the Pharmaceutical Inspection Convention treaty, which has been in force since March 1971. According to this treaty, when a product is imported, the importing country requests an inspection report from the country where the product was manufactured, and the importing country is obliged to accept the conclusions of the inspection report. However, this latter country maintains the final decision on the product or controls on reception. Unfortunately, no developing country can adhere to this treaty at present.

3.2.5. A long evaluation period leads to lack of flexibility

For example, the average time for evaluation of a file in France in 1995 was from 200 to 220 days.

3.2.6. Lack of quality guarantees in Europe for drugs without MA

Essential generic drugs manufactured in Europe for developing countries or humanitarian aid organizations currently do not all possess an MA, and only several have export declarations. These exported drugs are not evaluated as those having an MA, leading to confusion for importers and potential laxness for manufacturers. It should at least be necessary for manufacturers to deposit a pharmaceutical file with the administrative health authorities listing the important parameters regarding quality (raw materials, stability and bioequivalence studies), and they could then be inspected on that basis.

IV. PROPOSED STRATEGY

The first step should be to avoid calls for open tenders, even with stringent guidelines, and to prefer limited calls for tenders from a restricted list of qualified suppliers, via the audit/MA for the product (country of origin or imported)/quality control triptych.

1. Systematic audit of manufacture

1.1. Effective audit according to references of GMP

1.2. Documentary audit via site master file

- Organizational structure.
- Index cards stating duties of management and department heads.
- Plans of premises with ducts, divisions.
- Descriptions of air and water treatment.
- Important procedures (batch release, cleaning, validation of sterilization, batch recall).
- List of manufacturing operations with material used and controls.

2. Registration in the country of origin and on import

It is necessary to insist on developing mutual recognition of registration and inspection (simplification of procedures). Furthermore, any manufacturer who does not, for various reasons request an MA in his country of origin, should nevertheless deposit a file which would be evaluated and would contain, for example :

- part II of the MA file : stress quality of the raw material with a note that only raw materials with a DMF registered in a known country or certified according to procedures of the European Pharmacopoeia should be used ; give three potential sources for certified raw materials ; where official certification is absent, give technical specifications and commitment of manufacturer guaranteeing concordance of the quality of the raw material with the monography of the pharmacopoeia chosen as a reference ; manufacturing formula and if there is a change, an obligation to declare same description of manufacture ; tropical stability studies according to ICH3, for finished products,
- tolerance and acceptability studies if the product has never been administered in this formulation.

The importing country should obtain this file and the following information according to its own criteria :

- bioequivalence, if necessary, or, as the case may be, dissolution tests,
- bibliography for expected uses,
- no new uses other than those intended with the original speciality, except in demonstrations for clinical trials,
- medical information,
- labeling,
- samples.

To simplify, the exporting country should be able to guarantee drug quality in the broad sense, even if it does not have an MA, by evaluating the part II of the master file and inspecting the manufacturer on that basis. The importing country conducts evaluations according to its own criteria of safety and efficacy, most often by bibliographic studies for essential generic drugs, as well as information and directives for use by prescribers. This sharing of tasks allows different partners to share responsibilities and involvement.

3. Quality control at time of registration

Once the product has been registered, quality control is exercised in more random fashion, i.e. is part of an audit or inspection to avoid lapses in quality. Quality control is a most important tool in evaluating the quality of drugs.

4. Mutual recognition of inspections

Inspections by administrative authorities of countries where manufacturers are located must be conducted to be able to ensure conformity of products to references. It is not to be expected that developing countries' inspectors or humanitarian aid

associations will do this work. Developing countries should be encouraged to adhere to the PIC treaty. In addition, WHO makes these recommendations but has no power of control or coercion.

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Quality control is an important tool in the global evaluation of drugs. The manufacturer's audit, knowledge of the technical and pharmaceutical file of the drug and reference data are necessary parts of quality control. This is the only approach that can currently guarantee the actual quality, safety and efficacy of drugs. However, this approach has a price, and competition for supplies should occur among a panel of suppliers preselected by a set procedure and not by calls for open tenders.

Furthermore, the pharmaceutical responsibility of manufacturers must be effective in involving administrative authorities, who must guarantee quality for all drugs exported from Europe, to a greater extent. This policy, though difficult to implement on short notice, can standardize and rationalize the drug quality in the developing countries.

REFERENCES

1. L'utilisation des médicaments essentiels, 6^e rapport du comité OMS d'experts. - OMS, Série de rapport techniques, 850.
2. La situation pharmaceutique dans le monde. - OMS, Genève, 1990.
3. Code de la santé publique, code de la famille et de l'aide sociale.- Dalloz, Paris, 1995.
4. 34^e rapport du comité OMS d'experts des spécifications relatives aux préparations pharmaceutiques. - OMS, Genève.
5. Les échanges de médicaments entre pays européens et pays en développement: efficacité de systèmes de régulation, problèmes et perspectives. - Enquête menée par Pimed, Remed and Wemos sous l'égide de la commission européenne (DG VIII), ministère français de la coopération, mars 1996.
6. JUILLET Y. - Nouvelles dispositions sur l'importation et l'exportation des médicaments. - STP Pharma Prat., 5, 374-377, 1995.
7. ICH Harmonized Tripartite Guideline, - International Conference of Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use.
8. JOSSIN A. - Pratique du DMF en France et perspectives dans l'Europe communautaire. - STP Pharma, 1, 478-482, 1991.
9. LANET J. - La responsabilité pharmaceutique. - STP Pharma Prat., 5, 378-382, 1995.
10. GIRON D. - Influence de la qualité des matières premières sur la vitesse de dissolution et la biodisponibilité. - STP Pharma, 4, 330-340, 1988.
11. THEVENIN M. - Influence de la qualité des matières premières sur la vitesse de dissolution et la biodisponibilité. - STP Pharma, 4, 341-345, 1988.
12. LALOGÉ M., CHULIA D., GUILLEMOTEAU J.Y. and VERAIN A. - Incidence de l'origine des matières premières sur leurs qualités pharmacotechniques. STP Pharma, 4, 319-324, 1988.
13. RABIANET J. - Problèmes analytiques liés à la qualité des matières premières. - STP Pharma, 4, 237-241, 1988.
14. La procédure de certification de conformité à la Pharmacopée européenne. Pharmeuropa, 7, 2 juin 1995.
15. PELLERIN F. - Le suivi des matières premières de l'origine à l'emploi. - STP Pharma Prat., 5, 387-393, 1995.
16. JAMINET F. - Biodisponibilité des médicaments et équivalence générique. Labo-Pharma Prob. Tech., n° 294, janvier 1980.
17. Les essais de dissolution des formes solides pour voie orale. Mise au point biopharmaceutique et relations avec la biodisponibilité. Rapport d'une commission SFSTFT - STP Pharma Prat., 2, 500/506, 1992.
18. AIACHE J.M. and BEYSSAC E. - Corrélations in viro-in vivo : rêve ou réalité. STP Pharma, 6, 678-685, 1990.
19. Note for Guidance. Investigation of bioavailability and bioequivalence. - Commission of the European Communities. Committee for Proprietary Medicinal Products (CPMP), III/54/89, 1991.
20. ABELLI C. - Génériques humanitaires : intérêts et limites des cinétiques de dissolution dans le contrôle qualité des gélules. Application à la tétracycline et à l'indométacine. - Thèse doctorat pharmacie, Université Clermont-Ferrand, 1996.
21. PIOT 5. - Médicament essentiel multisource : étude de stabilité en conditions réelles. - Thèse doctorat pharmacie, Université Clermont-Ferrand, 1997.
22. MELE E - Vers l'introduction de la libération paramétrique dans la pharmacopée européenne. - STP Pharma Prat., 6, 85-88, 1996.
23. RIDOLPHI-REBHUNN 5. - Certification de la qualité des médicaments. Etude de deux approches : le système OMS et la certification ISO. - Thèse doctorat pharmacie, Université de Strasbourg, 1995.
24. LE HIR A. - Normes ISO 9000 et BPF. - STP Pharma Prat., 3, 388-395, 1993.
25. Bonnes pratiques de fabrication, juin 1995. - Agence du médicament et ministère de la santé publique et de l'assurance maladie, Direction des Journaux officiels.
26. NOUALHAC H. - Responsabilité pharmaceutique dans les échanges internationaux : principe et vécu. - STP Pharma Prat., 5, 383-386, 1995.
27. 32^e rapport du comité OMS d'experts des spécifications relatives aux préparations pharmaceutiques. - OMS, Genève.

