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MARKETING AUTHORIZATION OF PHARMACEUTICAL PRODUCTS WITH SPECIAL REFERENCE TO MULTISOURCE (GENERIC) PRODUCTS: A MANUAL FOR DRUG REGULATORY AUTHORITIES

Preface

This text was developed in consultation with national drug regulatory authorities within WHO's Member States. The draft was circulated for comment and discussed at two informal consultations convened by the WHO Division of Drug Management and Policies in Geneva from 7 to 8 April and 6 to 8 July 1998. Contributions were made by.

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I. INTRODUCTION

As outlined in WHO's Guiding Principles for Small National Drug Regulatory Authorities (*1*) an important task for a drug regulatory authority (DRA) is to institute a system which subjects all pharmaceutical products to premarketing evaluation, marketing authorization and postmarketing review to ensure that they conform to required standards of quality, safety and efficacy. Because it has responsibilities in public health, in most countries the DRA is located in, linked to or reports to the Ministry of Health. This manual is intended to provide guidance to countries which do not already have a fully functioning system of premarket evaluation and market authorization, and have a particular interest in the assessment and authorization of multisource (generic) pharmaceutical products. Many of the principles apply to other groups of medicines (such as complex biologicals and 'alternative' preparations), but the details may be specific to multisource products.

For the purposes of this manual, the term *drug regulatory authority* means a network that administers the full spectrum of drug regulatory activities, including at least the following functions and others:

- Marketing authorization for new products and variation of existing authorizations;
- Quality control laboratory testing;
- Adverse drug reaction monitoring;
- Provision of drug information and promotion of rational drug use;
- Good Manufacturing Practice (GMP) inspections and licensing of manufacturers, wholesalers and other distribution channels;
- Enforcement operations;
- Monitoring of Drug Utilization.

In some regulatory systems the functions of an individual DRA may be more limited. The manual may still be used when, for example, the DRA is confined to marketing authorization activities.

This manual provides detailed guidance on the structure and operation of those functions of a DRA that deal with premarket evaluation and marketing authorization, also known as *drug registration.* The other activities are a necessary complement to the marketing authorization function but are not discussed in detail in this document. The principles underpinning premarket evaluation and the marketing authorization process are discussed in WHO's Guiding Principles for Small National DRAs (*1*).

The advice in this manual is intended to be independent of local political and legal structures. Instead of being prescriptive, it describes options from which governments can select the most suitable path, depending on current circumstances.

Marketing authorization applications can be classified broadly in three groups, which comprise applications for:

1. Products containing new chemical or biological active pharmaceutical ingredients (APIs);
2. *Multisource pharmaceutical products (generic products):* that is, new marketing authorization holders, formulations, or sources of *well established drugs*;
3. Variations to existing marketing authorizations.

Evaluation of the complex toxicological and clinical data which accompany new chemical entities requires resources and experience that are usually found only in national DRAs with substantial funding and skills. Countries with more limited resources may wish to give

priority to *well established drugs*. They can then await the outcome of detailed premarketing evaluation
of safety and efficacy, and postmarketing surveillance of safety, by the well resourced authorities before considering issuing marketing authorizations for newer drugs (see Part III "Collaboration with other DRAs"). If a *new drug* appears to be important for an endemic disease, a report may be available on request from one of the well resourced DRAs. If not, WHO is usually able to provide technical advice.

A number of existing WHO guidelines that are directly relevant to this manual are reproduced in full as Annexes. Updates of these guidelines are issued from time to time, and it is the current issue that will usually be the most relevant. Key terms used in the manual are defined in the Glossary.

II. PROVISIONS AND PREREQUISITES FOR REGULATORY CONTROL

A. Political will and commitment

No DRA will be successful in implementing these guidelines if it does not have full and continuing government support, even when the government changes. The government must provide:

- Clear, firm, and equitable legislation that addresses all the relevant issues and carries appropriate sanctions for violations (see Annex 1);
- Support in the form of financial and other resources that are commensurate with the designated functions, particularly in relation to staffing and the resource needs for the GMP inspectorate and quality control laboratories;
- Advocacy in the political arena, and particularly a willingness to defend decisions and policies which may be unpopular with vested interests but which are to the benefit of public health;
- Support when legislated sanctions are imposed for violations of legislation.

The relevant political authority is usually the Minister for Health but may be a person or persons under a different title, depending on the country's legislative system.

The appropriate level of financial support depends on what functions the government intends the DRA to undertake. If an authority is expected to review only *well established drug products*, not products containing new chemical or biological APIs, and to rely mainly on decisions made by DRAs in other countries, it would be reasonable for financing to be sufficient for only these functions, with further allowance for the evaluation of interchangeability and of locally developed and manufactured products. More extensive responsibilities would require additional resources. A system of fees for evaluation of applications and subsequent *retention fees* to maintain the marketing authorization is one means of recovering costs and is further discussed below.

The budget should be subject to adjustments according to the resources required for the DRA's functions as they evolve.

A number of decisions of principle must be made by government at a very early stage (see particularly Part II "Rational selection of drug products", and Part IV "Initial decisions on options
for premarket evaluation"). These decisions should be issued in writing, and should not be changed so often that a coherent and consistent approach becomes impossible.

Provisions and prerequisites

B. Legislation

The minimum provisions required for national drug regulatory legislation are set out in the guiding principles reproduced as Annex 1.

C. Accountability

Accountability means being required to account for one's conduct and actions, usually to an individual or group but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and *transparency.*

Because the field of medicines is highly commercialized, it is characterized by extreme pressures on the DRA and by intensive lobbying from stakeholders at many levels. A system of accountability is essential in managing these tensions. A DRA is usually accountable to an individual official, such as the Minister for Health, or to a body, such as the parliament.

Mechanisms for ensuring accountability include:

- A requirement to provide public reports on a periodic (e.g. annual) basis;
- Publication of decisions, processes and policies;
- A mechanism for appeals against DRA decisions;
- A procedure for complaints about the actions of the DRA and the conduct of individual staff;
- A code of conduct describing the behaviour expected of DRA staff;
- Regular presentations at government hearings;
- Formalized mechanisms for consulting independent experts;
- Public hearings on new policies, or on applications to register new pharmaceutical products or products containing new APIs. It should be borne in mind that public hearings can be expensive and time-consuming;
- Electronic publication of information about the DRA;

It is not necessary to implement all the mechanisms. The appropriate mechanism(s) will depend on the local context, but should be defined and recognized by the government and the DRA in published documentation.

Codes of conduct Some governments have general codes of conduct for government officials, while others have specific codes for particular agencies. A number of Internet webSites contain suitable guidelines, including these:	
www.icac.nsw.gov.au	Independent Commission Against Corruption, Sydney, NSW, Australia
www.oecd.org/puma/ gvrnance/ethics	Organisation for Economic Co-operation and Development, Strasbourg, France
www.ethics.ubc.ca	University of British Columbia, Vancouver, Canada
www.usoge.gov	US Office of Government Ethics, Washington, DC, USA

D. Resources for the marketing authorization function

Definition of responsibilities

As noted above, ultimate responsibility for the marketing authorization function lies with the country's government. The minimum necessary activities are as follows:

- Establishing and maintaining an inventory of the products available on the local market;
- Premarket evaluation of new products:
  - Ensuring that a complete data-set on quality is available;
  - Evaluating, as appropriate, either data on quality or relying on a WHO-type certificate (see glossary and Annex 2);
  - Ensuring that newly authorized products containing well established drugs are interchangeable (as defined in Annex 3) with locally marketed products, and that the approved product information is accurate and locally useful;
  - Issuing a written marketing authorization (or rejection) on completion of the assessment process.
- Evaluating applications to make changes to product information and to pharmaceutical aspects of existing marketing authorizations;
- Noting possible breaches of legislation and referring them to the investigatory arm of the DRA.

In addition to marketing authorization activities, DRA staff may be given responsibilities such as promotion of rational drug use, provision of drug information, control of company promotion, monitoring of adverse drug reactions, publication of information on pharmaceuticals (e.g. a newsletter), and studies of drug utilization to enhance rational drug use and assess the impact of regulatory decisions. In some countries, the cost of a product may be a consideration in reaching a decision on marketing authorization.

As already indicated, resources provided to the DRA for performing marketing authorization activities should be consistent with the defined responsibilities.

Staff

Skills

Decisions concerning quality, therapeutic equivalence and product information labelling must be taken by persons with suitable knowledge and practical experience of the subject. The quality control of drugs requires a knowledge of pharmacy and chemistry. Evaluation of therapeutic equivalence and product information labelling requires a knowledge of the uses and safety of medicines. As a minimum, evaluators of therapeutic equivalence and product information labelling should be qualified in pharmacy, clinical pharmacology, medicine or a similar discipline, and have practical experience in at least one of these disciplines. It is desirable for evaluators of therapeutic equivalence to have practical experience of biopharmaceutics. While external expertise should also be available (see below), the authority's own staff must be capable of understanding and implementing the expert advisory body's recommendations (see below "Expert advisory body"), acting on information made available by WHO or other DRAs as aspects such as safety, and quality, and taking action on their own initiative in a crisis.

Some part of the DRA needs the capacity, including staffing, to investigate possible breaches of legislation and, if necessary, to initiate action in the courts in cooperation with legal officers. A knowledge of the local judicial procedures and legislative process is essential. The DRA itself need not have a full-time lawyer but must have access to legal advice in relation to its functions.

Provisions and prerequisites

Any organization needs the skills of competent administrators. The scientific and medical experts should be complemented by a suitable number of administrative staff, including computer specialists or access to them. A DRA has a particular need for persons experienced in handling large quantities of documents and daily correspondence, which may need to be retrieved at short notice.

Training

Scientific and medical skills must be continuously updated to keep pace with drug discovery and development, including the development of new means of formulating, controlling and using wellestablished drugs. It is therefore essential for suitable training and practical experience to be offered regularly to the staff concerned. WHO is able to provide assistance in finding places for such training.

Numbers

The number of staff to be employed in marketing authorization activities should be determined by the responsibilities to be undertaken. The major determinants of staff numbers are these:

- The degree to which the authority is prepared to rely on decisions made, and reports prepared, by well resourced authorities in other countries;
- Whether there is a local pharmaceutical industry in the country, and hence whether there are local products for which a suitable foreign evaluation will not be available;
- The number of products to be processed.

In addition, if there is no current list of pharmaceutical products authorized for marketing, also known as the *register*, appropriate additional resources will be essential for its preparation.

A regulatory "culture"

The DRA should cultivate an attitude among its staff of independent thinking, impartiality and pride in their work. Everyone in the organization should be motivated by a desire to ensure that effective, safe and good-quality drug products are available to the public in adequate quantities and are used rationally. It should be clear that staff at whatever level who succumb to favours from outside sources are damaging the reputation of the whole organization, including that of their colleagues.

Premises

Data submitted by applicants for marketing authorizationshould be stored with sufficient security to give the applicants the confidence that they cannot be subject to theft or unauthorized copying. To the extent possible, premises should be fire- and water-proof.

Professional staff whose responsibilities include sustained periods of concentration will perform more efficiently (in terms of output and reliability) in quiet surroundings.

Archiving

Access to earlier documents is essential for technical, legal and political reasons, and must be

considered at the time the data are first stored. Electronic archiving has considerable advantages in terms of information retrieval, but is not yet sufficiently durable and reliable. For the foreseeable future, electronic archiving should be backed up by storage of paper copies.

Computers

Given the numbers of applications likely to be processed by a DRA, the quantity of information associated with each, and the frequent need for rapid retrieval of information , computerization is the most viable means of recording and keeping track of applications and marketing authorizations. The process of keeping a record of the progress of an application at all stages and of the status of marketing authorizations is known as tracking. These are some examples of the information that a computerized system can provide:

- The progress of a particular application for marketing authorization;
- All premises for which a GMP inspection is due;
- Applications which have been awaiting evaluation for a given period of time, say three months;
- The reference number or date of the currently approved product information;
- Details of previous decisions taken on the same or similar active ingredient;
- A list of marketing authorizations due to expire over the next 12 months.

Applications for variations should also be listed on a computerized system, even if their progress is too rapid for tracking to be valuable. However, this will permit retrieval of information on variations after they have been made.

The country's register of authorized drug products is most easily maintained in electronic format, The data set can then be quickly searched for information of the type mentioned below under "Inventory of existing products on the market".

Access to the Internet is of immense value, both for e-mail communication with the staff of other DRAs and to obtain information from web sites. Some well resourced DRAs have a home page which the smaller national authorities will find invaluable as a source of information.

The costs and benefits of computerization are discussed in detail in a WHO document on *How to introduce computer-assisted drug registration* (*2*). The WHO manual entitled *A model system for computer-assisted drug registration. User manual* (*3*) should also prove useful.

Expert advisory body

In any country, whether or not the DRA has extensive resources, maximum advantage should be taken of local expertise available in universities, research institutes, teaching hospitals and primary health care facilities. This is usually achieved by setting up an expert advisory body which meets on a regular basis to provide advice to the DRA. Membership should include individuals with the highest available scientific expertise so that their advice is seen by the community, health workers and the government as authoritative and credible. The scope of issues to be discussed will determine the expertise required, but it should normally include pharmaceutical chemistry, pharmaceutical technology, pharmacokinetics/bioavailability, pharmacology, clinical pharmacology and medicine. DRAs that intend to evaluate toxicological data will in addition need experts in that area. Members should include both those with up-to-date theoretical knowledge and those with practical experience, especially in

quality control, clinical medicine and the conduct of bioavailability/bioequivalence studies. Pharmacists with experience of pharmaceutical distribution, and primary health care physicians, should be included in the expert advisory body to provide practical advice.

If members of the expert advisory body are given membership for a fixed term, their advice is less likely to be dependent on political considerations.

The practical role of such a body varies. Some DRAs seek advice only applications on marketing authorizations concerning new chemical entities. On the other hand, a newer and/or smaller DRA may chose to refer all interchangeable products which are to be evaluated in full to the advisory body, at least until sufficient experience has been gained to serve as precedent and guidance for the future. Equally, a DRA may request the expert advisory body to lay down broad technical policies so that only difficult applications need to be referred. In addition to giving technical advice, such a body can be constituted so that it provides up-to-date information on the local clinical situation, for example in relation to microbial resistance or the prevalence of endemic diseases. The expert advisory body can also be a source of advice as to whether a particular drug is essential in the local context (see below - Rational selection of products), but it is better for this function to be performed by a separate body or committee if resources permit.

It is a matter for local legislation whether final responsibility for marketing authorization decisions lies with the expert advisory body, or with the DRA on advice from the expert advisory body. The legal position, whatever it may be, should be made clear to all parties.

Decisions of the advisory body need to be transparent. In practice, this means that reasons should be given for all decisions.

If the expert advisory body is to review applications for new marketing authorizations or variations to existing ones, it is inappropriate to appoint people who are currently employed by the pharmaceutical industry as members because this would give rise to a conflict of interest. Members should in any case sign a declaration that they have no conflict of interest before participating in the activities of the expert advisory body. Annex 4 contains a model form for this purpose, together with guidelines (for both experts and DRAs) as to what constitutes a conflict of interest.

It should be noted that paragraph 2 of the model statement inAnnex 4 allows (among other things) for a member to declare that he or she has a conflict of interest in relation to a particular item in an agenda. The DRA (or the committee's chairman) may permit the member to withdraw from consideration of that item but remain as a member of the committee for other purposes. Such declarations should be recorded, for example in the committee minutes.

Financial support for the DRA should include provision for the expert advisory body. Expenses may include reimbursement of members' travel and accommodation costs if incurred. Remuneration for loss of income should not be excessive and should not be related to the outcome of the evaluation.

E. Fees and cost recovery

Several countries impose fees for the evaluation of applications for new marketing authorizations. Some countries also impose retention fees (usually annual) after the authorization has been granted. As well as contributing to cost recovery and therefore to better drug regulation, application fees discourage applications that may never result in a marketed product (applications which "test the water"). The fees should be collected by the DRA and used to fund regulatory activities.

Fee income could allow for staff numbers to be adjusted to match the current workload. At times when the number of applications is high the income from fees will be higher and more staff can be employed. It takes time and resources to train the additional evaluators. When application numbers are low, therefore it is better to redeploy them (for example as GMP inspectors) rather than dismiss them, so that they are available for future periods of high work flow.

If fees are imposed, they should be high enough to contribute significantly to the efficient and effective functioning of the DRA. Application fees relate to the cost of the marketing authorization system, while retention fees relate to the other functions of the DRA, such as postmarketing activities. Whether fees are set high enough to recover all or only part of the DRA's costs, should be determined by the government. If only part of the costs are recovered, the remainder is usually funded by the government from general revenue.

Some DRAs have been asked to generate their own income by undertaking activities which yield a profit, usually by means of consultancies. Examples of consultancy services for profit include acting as a commercial testing laboratory, providing advice to other governments and agencies, and providing advice during legal proceedings. Conducting such activities for profit is contrary to the purpose and ethic of a regulatory agency, distracts from the regulatory function and should be discouraged. However, provision of such services on a cost-recovery basis is acceptable, for example for training activities and the supply of publications.

Fees are usually set on the basis of the work that the application will generate, i.e. the nature and amount of data to be analysed. Fees for applications for multisource products are usually lower because they require less assessment work. Fees can also be adjusted to achieve national goals. For example, provision can be made for reducting or exempting fees for vital drugs with a limited market, and/or annual charges can be made proportional to gross annual sales. Application and retention fees should not normally be different for imported and locally produced pharmaceuticals. However, some countries with developing economies have reduced fees for local companies to promote local production.

The scale of fees should be published, including any variation applied to local products. Thus the fee structure should be transparent and fees should not vary in individual cases.

F. Inventory of existing products on the market

Important as it is to evaluate new products prior to marketing, the marketing authorization process and control of quality, safety and efficacy are compromised if the DRA cannot identify products that are already being marketed without prior approval. It would be inequitable for applicants that have generated scientific documentation and submitted their products to the authorization process to be penalized by delays in reaching the market, expenditure of resources

and payment of any fee that is in place, as compared with manufacturers who have not sought premarket approval.

The market inventory needs to be conducted only once, shortly after the marketing authorization system is established. It is normal to issue a *provisional marketing authorization* at this point, and to conduct a review (or screening) of provisionally authorized products as soon as possible. All manufacturers and importing agencies must be given reasonable notice through official publications (e.g. gazettes), the trade press and other media of their obligation to notify the authority by a specific date of all medicinal products that they currently distribute within the jurisdiction of the authority and that they intend to continue to supply after a duly appointed date on which licensing requirements become effective (*1;* see also Annex 1).

Once completed, the inventory consists of a printed text and/or electronic database. The information it should contain and the subsequent review of provisionally authorized products are discussed in Annex 1. Essentially the data set comprises pharmaceutical, clinical and administrative information about the product. *The model system for computer-assisted drug registration* (*2* and *3)* includes provision for an inventory.

Knowledge of what is already on the market has a number of benefits for public health, including:

- The ability to produce a list of products manufactured at a site found to be unsuitable by GMP inspectors;
- Ready access to a list of products containing a particular substance(s) when a hazard from that substance(s) has been detected;
- Knowledge of competing products for pricing purposes.

It is a major task to build a complete inventory of a hitherto unregulated market and most countries undertake it in stages. It should be undertaken in parallel with the introduction of premarket evaluations and authorizations; a short delay in commencing the inventory quickly becomes a long delay.

Among the first steps in conducting an inventory is to obtain an estimate of the number of products that may require provisional marketing authorization. It can be difficult to arrive at even a reasonably accurate figure, and the total may be dauntingly large. Experience has shown, however, that with each step taken by the DRA in conducting the inventory and accumulating data for the subsequent review, significant numbers of products are voluntarily withdrawn (*4*). These are likely to be products of marginal viability which do not warrant expending company resources on preparation of the necessary documentation and generation of data on, for example, stability. Some of the products may not even be marketed, but have simply been kept on file as an option for the future.

G. Rational selection of products

Public health need

Each country must first decide, as a part of its health policy, whether it intends to allow a large number of drugs to be authorized, or instead to concentrate its financial and distribution resources on a smaller number of drugs which it considers essential in the light of public health need. In the first case, a company may submit an application for marketing authorization for *any* new product with proven quality, safety and efficacy, without considering whether it is essential for public health. In the second case, marketing

authorizations are not issued for drugs which are deemed non-essential in the light of, for example, the WHO Model List of Essential Drugs (5) and of local requirements and public health needs, notably in relation to endemic diseases. In both cases, new products must be subject to an application for marketing authorization and a process by which a decision is made as to whether the product meets appropriate standards of quality, safety and efficacy, product information and, when applicable, therapeutic equivalence.

For countries with limited financial and distribution resources, drugs that are essential to public health must be a priority. Availability of essential drugs with a small potential market can be encouraged by, for example, waiving the initial application fee and not charging a retention fee.

These decisions guide the functioning of the DRA. Whatever approach the government chooses to take must be defined in both the legislation and in the DRA's guideline documentation.

Number of interchangeable products

A separate decision is needed on whether any number of licence holders may be authorized to market the same active ingredient, or whether the number for each should be restricted. This is a decision that each country must make on the basis of the local situation. Some of the factors are set out below:

In favour of limiting the number of licence holders

- More resources are needed for premarket evaluation of multiple licence holders prior to issuing marketing authorization, GMP inspection, and subsequent quality control laboratory testing to detect substandard and counterfeit products.
- More resources are needed for distributing and holding stocks of several licence holders' products than for dealing with a more limited number, particularly in terms of administrative records.
- Multiple licence holders stimulate competitive promotion, leading to more pressure on pharmacists and prescribers and possibly to unnecessary prescribing.

Against limiting the number of licence holders

- In the absence of price controls, price competition among multiple licence holders can be encouraged, which may - depending on local circumstances - lead to a lower prices.
- The existence of multiple licence holders can stimulate local economic growth and hence employment.
- In addition to the potential for lowering price, competition promotes manufacturing efficiency, and possibly even quality if regulatory controls are comprehensively applied and enforced.
- Enforcement of regulations becomes difficult if only one brand is authorized (i.e. has a monopoly) and the drug is essential. The DRA may then have to decide whether to allow substandard batches to remain on the market, or to interrupt supplies of an essential drug.
- If only one brand is authorized, failure of that source (e.g. because of a fire at the site of manufacture or a decision to discontinue marketing) means that the drug is no longer available.

Provisions and prerequisites
If it is decided to limit the number of licence holders, in keeping with the principle of transparency, criteria for granting marketing authorizations should be published and the reasons given for any negative decisions.

Price

Pricing is a complex and political issue on which WHO has published widely (e.g. *6*-*8*). In some DRA, evaluation of price is still a part of the marketing authorization procedure, but in others it is a separate process handled by reimbursement or insurance agencies, which may be public or private. Although pricing policies are not discussed here, the following points are relevant:

- A low price does not justify accepting supplies that are of inadequate quality, safety and efficacy.
- While some governments take price into account, others consider this separately from the assessment of quality, safety and efficacy.

H. Special access schemes

Legislation should allow access to *unregistered drug products* in special or emergency situations. In general, either the patient has a severe or life-threatening illness and existing therapy has failed, or the disease is a rare one for which specialist medicines do not have a local marketing authorization. In many cases the drugs are still experimental, or at any rate unproven, and the government is not obliged to fund their supply. Care is necessary in the administration of these schemes to avoid de facto marketing.

I. Postmarketing activities

Having satisfied itself that it has in place a reliable system of premarket evaluation, the DRA must ensure that the standards required are maintained. As far as resources allow, postmarketing activities should include:

- Review of applications to vary authorized products;
- Random audits of notified variations (see Annex 10);
- GMP inspections of local manufacturers;
- Quality control laboratory testing of samples selected randomly;
- Quality control laboratory testing of samples suspected to be substandard;
- Monitoring of adverse drug reactions;
- Monitoring of advertising and other promotional activities;
- Promotion of rational drug use;
- Monitoring of the implementation of the regulatory component of the national drug policy;
- Drug utilization studies.

Priorities within this list may vary in different countries.

III. OPERATING ACTIVITIES

A. Transparency

Transparency means (1) defining policies and procedures in print and publishing the printed documentation, and (2) giving reasons for decisions to the party concerned. DRAs should adopt a policy of transparency because it is the simplest and most efficient way of conducting

business. While the circulation of some documentation may need to be restricted, for example during policy development, the majority of finalized written documents (and particularly those concerning policy and administration) should be made available to DRA staff, the pharmaceutical industry, the parliament and the general public. DRAs with limited resources may achieve cost savings by posting their guidelines on the Internet. Transparency has these advantages:

- Applicants and the DRA do not spend time trying to clarify each other's policies and attitudes.
- Staff within the DRA do not spend time determining what their own agency's policies are ("reinventing the wheel").
- Communication at all levels is facilitated if each party understands the other's starting point for discussions.
- Terminology is defined in policy documents so that the parties use the same terms to mean the same thing.

Transparency also means giving reasons for decisions. For example, letters rejecting applications should include reasons for the decision.

B. Policies

General policy should be documented and published. Policy documentation may specify, for example:

- Situations in which data on bioequivalence are required;
- Whether and under what circumstances evaluation reports prepared by another DRA will be accepted;
- Which fixed-dose combinations are considered rational, safe and effective.

The advantage of such "in principle" policies is that decisions on individual applications become easier and less time-consuming.

C. Administrative procedures

Administrative procedures should be documented and published. Correspondence and data are far less likely to go astray when clear procedures are in place. It is particularly important that all DRA staff have copies of administrative documentation and understand their own role in the procedures.

If pharmaceutical companies have access to the written administrative procedures, they will better understand how to submit applications, whom to contact when they have questions, and how to respond on receipt of correspondence. When they have an inquiry, they can ask more precise and sensible questions. The industry and DRA staff should be informed of the appropriate lines of communication.

D. Guidelines for applicants

In keeping with a policy of transparency, the DRA should publish guidelines on the data to be provided with the different types of applications. It is not necessary to write a completely new guideline when several such documents exist worldwide. The simplest approach is to adopt the content and format of an already existing guideline, such as that of Canada, the European Union (EU), Japan, South Africa, the United States Food and Drug Administration (FDA) or the International Conference on Harmonisation (ICH) (see box) with, if necessary, modifications to accommodate the local situation. More than one guideline can be adopted, in

which case applications may follow either guideline. It will often be appropriate to add technical requirements appropriate to local circumstances, such as requirements for higher temperature and/or humidity data to reflect the climate, or for interchangeability. WHO guidelines are available on most of the technical requirements for multisource pharmaceutical products.

Harmonization of technical guidelines is a desirable goal for following reasons:

- Companies have to generate only one data set for all regions, and consequently the amount of human and animal experimentation is reduced;
- The cost of development of new drugs is reduced, which ought to lead to lower price;
- Local products are more likely to be acceptable for export to other countries.

Some additional experimentation may be necessary for local purposes. For example:

- Studies on interchangeability with locally available products;
- Stability studies under conditions of high temperature and/or humidity (see Annex 11) to verify local applicability;
- Clinical and/or toxicological studies in support of use in endemic diseases;
- Special studies in ethnic groups.

Such studies may be conducted in another country provided that they directly address the local issues and are of a good scientific standard.

> ICH (the International Conference on Harmonisation) is an initiative supported by regulatory and industry associations from the three major economic areas of the world, namely the USA, the European Union and Japan. Other parties, such as WHO and the European Free Trade Association (EFTA), are observers. ICH produces guidelines on data requirements for marketing authorization of new chemical entities and biologicals for use in the member regions of ICH. These guidelines are sometimes adopted by other countries for reasons of harmonization.
> Other regional groupings are in the process of building up similarly harmonized guidelines, including the Association of South-East Asian Nations (ASEAN) and the Convenio Hipólito Unanue (an agreement between a group of South American nations).

The guidelines on data to be submitted should be interpreted in a flexible manner. There may be means of establishing quality, safety and efficacy other than those in the guidelines. A general guideline may not be applicable to a particular product. Applicants should have the option of presenting data that are not in conformity with guidelines, but the onus is then on the applicant to demonstrate, by science and sound argument, that the alternative is acceptable. It is not the DRA's responsibility to make the best of poor data. The DRA should be able to refuse applications which do not meet the guidelines if the case been argued is not sound.

It is usually appropriate to combine guidelines on technical data with those on administrative requirements in a single publication. Technical and administrative guidelines should be readily available on request by potential applicants. A fee may be charged, depending on government policy.

E. Model application form

Annex 6 contains a model application form for marketing authorization, with notes to the applicant.

F. Communication among departments within the DRA

For maximum efficiency, the various components of the DRA must function as an integrated whole, or team. Regular meetings of the leaders of the different departments, each presenting short progress reports and news items, ensure that all areas are aware of each other's current activities. New activities should be agreed by the department as a group and not by individual areas in isolation. This includes setting priorities, for example among those listed as minimal for the marketing authorization function in the section on "Definition of Responsibilities" above.

Examples of the types of operational interaction that can be beneficial are given below.

G. Relationship of evaluators with GMP inspectors

GMP is recognized as a vital component of the control of pharmaceuticals. All sites of manufacture for new marketing authorizations, and new sites for existing products, should be cleared with respect to GMP, either by the DRA's own inspectorate or by means of a WHO-type product certificate from the country of manufacture. Whether local sites are given a general inspection, or whether a separate inspection is conducted for each new marketing authorization, is a matter for local legislation or policy. At least finished-product manufacturing sites should be certified. Guidelines are currently being developed with a view to establishing WHO-type certification of sites at which an API is produced.

DRAs should encourage communication between evaluators and the GMP inspectors. An evaluator reading a dossier must ultimately take on trust much of what the company states, for example that certain equipment is available and is used. An experienced evaluator can sometimes detect discrepancies in the data set that suggest misrepresentation or even outright fraud. In these cases, a GMP inspector is in a position to follow up the evaluator's queries, and should do so. The inspector and the evaluator should discuss whether the discrepancy is sufficiently critical to warrant site inspection prior to issuing the marketing authorization, or whether it can wait until the next scheduled inspection of the site.

Even when a discrepancy has not been detected, GMP inspectors should make random checks during routine inspections to verify information submitted with applications.

H. Relationship of evaluators with the quality control laboratories

Quality control laboratory testing should be available as a part of the premarket evaluation process. It is essential that a sample be tested if the DRA has been unable, for whatever reason, to conduct a full evaluation itself. Quality control laboratory testing should also be available in cases where the evaluator has reason to question the information provided, for example to check whether an assay method will in fact work.

The sample subjected to testing should comply in all respects with the information submitted for premarket evaluation, including formulation, method and site of manufacture, quality control, and so on.
If there is no national quality control laboratory, or if the country in question lacks the facilities to test the product (e.g. because special equipment is required), contract testing by another DRA or by WHO interregional or regional laboratories is acceptable. Where national quality control laboratories do exist, operational links with peripheral laboratories (both public and private) can enhance geographical coverage.

Operating activities
Quality control laboratory testing of products that are already marketed, followed up by strong action when quality is found to be poor, encourages manufacturers to maintain product quality.

I. Functional relationship of the evaluators with the expert advisory body

The functions of the expert advisory body (see above) and the types of application to be referred to it should be defined in writing. The DRA normally provides the advisory body's secretariat, and keeps records of the matters discussed and its recommendations.

To take maximum advantage of the expertise available on the expert advisory body, members of this body must feel free to provide independent advice.

J. Relationship of evaluators with the pharmaceutical industry and confidentiality of data

General

A balance must be achieved in relationships with the pharmaceutical industry. While the industry can assist the agency by providing useful comments on guidelines and administrative procedures, the DRA ultimately has responsibility for decision-making. Relationships with industry associations and individual companies should be cooperative and friendly, but the DRA must be seen to be impartial and must guard its independence carefully. Any sign of favouring one or more companies must be avoided.

It is perhaps self-evident that an adversarial relationship between the industry and the DRA is unhelpful and contrary to the public interest. However, this has sometimes happened and efforts should be made to avoid it.

When discussion of draft policies is necessary, it is helpful if there is an industry association to which the majority of companies belong. Some countries have one association for local companies and one for subsidiaries of foreign companies. Consultation with each of these associations avoids the impression that a particular company or group is being favoured.

Informal communications with an applicant towards the end of an evaluation can both save time and avoid recourse to legal channels.

Confidentiality of data

Companies submitting data to the DRA are entitled to expect that those data will be held in to the extent allowed by local legislation and in accordance with the DRA's responsibilities. However, DRAs should not comply with demands for undertakings of confidentiality which seek to limit the lawful use or release of information. What constitutes such lawful use or release depends on local legislation. Examples of what is usually lawful in the exercise of the DRA's responsibilities include:

- Release of certain information to other DRAs and to WHO, especially information relating to safety;
- Release of documents in accordance with legislation on freedom of information where such legislation exists. There is normally an opportunity for the supplier of the documents to appeal against a proposed decision to release them;
- Access to earlier records, for example during the evaluation of applications.

Each DRA should ascertain its responsibilities and obligations in relation to confidentiality (e.g. in respect of international treaties) and should publish this information, for example in its guidelines for applicants.

Companies sometimes attach a declaration of confidentiality to each application. These are acceptable provided that they do not conflict with the DRA's responsibilities. If a data set includes a declaration of confidentiality that seeks to limit lawful use or release of information, the DRA should not accept the data set. An example of a declaration that is acceptable in some legal jurisdictions is:

> This submission is commercial and is privileged and/or confidential. It contains valuable data and/or information which is used in business and is of a type customarily used in confidence, or regarded as privileged, and has not been disclosed to any member of the public by [*name of the company or applicant]*.

Progress of applications

Understandably, applicants are often anxious to ascertain the progress of an application, whether for a new marketing authorization or for a variation. While DRAs may wish to be cooperative, providing this information can be resource-intensive and some individuals can be unduly persistent.

It is more efficient for DRAs to establish a predetermined and well publicized mechanism for dealing with such enquiries. These are some of the options.

- Do not allow them. This option may be the only resort in circumstances of limited resources.
- Allow enquirers limited on-line access to a computerized tracking system. This option has the major drawback that it facilitates access by “hackers” to parts of the database to which access is not intended, and even to different databases on the same computer. The option is not recommended.
- Publicize a telephone number to which enquiries may be directed. The telephone may be answered either directly by a staff officer, or by a telephone message system which is checked regularly, usually daily. This option is suitable if resources permit.

K. Meetings with applicants

Meetings between the DRA and applicants can be helpful to both parties. They can minimize delays and correspondence, clarify misunderstandings, and avoid expensive and time-consuming legal proceedings. However, the authority must maintain control over the venue, conduct and content of the meeting.

Because the authority must maintain its impartiality, meetings should normally take place on its premises. It is useful for more than one member of staff to be present so that (1) subsequent misunderstandings can be resolved and (2) any perception of conflict of interest or bias is avoided. A staff member of the authority should normally chair the meeting. It is also useful for the authority to prepare a brief note fore the file outlining decisions taken and any departures from normal (written) policy. Future disagreements can be avoided if a copy of the file note is forwarded to the applicant company.

The party requesting the meeting should list the issues to be discussed in writing and these should be agreed in advance. The list need not be more than a few items. The authority is not obliged to agree to a meeting if it feels that the issues have already been dealt with or are

adequately outlined in documentation available to the company.

The subject of such a meeting could include:
- The content of an application in a specific situation;
- Data requirements for a new type of product;
- Feedback to applicants on the reasons for failure of a particular application or applications;
- An enquiry from a new applicant that has not previously prepared a marketing authorization application;
- The discussion initiated by the DRA of inconsistencies between submitted data and information obtained by a GMP inspector.

It is prudent not to consider new data at a meeting, but to evaluate them separately. If any existing application has already been rejected, the new data may constitute a new application.

L. Procedures for appeals

Appeal procedures should be laid down in the legislation (see Annex 1) and administrative details should be described in the DRA's guidelines for applicants (see above).

Informal appeal mechanisms can also be made available and described in policy guidelines. These are often effective and they avoid the need for legal processes, which are costly and time-consuming for all parties. In their simplest form, the DRA may wish to encourage applicants to telephone and discuss decisions with the decision-maker. If necessary and useful, a meeting can be set up as described above. In appropriate cases, and where available, professional mediation may avoid the need for legal action.

M. Collaboration with other DRAs

Some DRAs choose to rely on decisions made by DRAs in other countries, while others use scientific reports prepared by other DRAs.

If the decision of another DRA is adopted, it is nevertheless essential for certain minimum information to be available. This is further discussed below (see sections "Initial decisions on options for premarket evaluation" and "Evaluation of data on quality" under Part IV).

The use of scientific reports prepared by experts in other national authorities does not necessarily mean automatically adopting the decisions made by other authorities. When a well prepared scientific report is available, a small DRA may be in a position to make its own decision in the light of local circumstances. With experience and a readiness to listen to feedback from local health workers, the utility of local decisions will improve.
Some agencies share in the preparation of reports while maintaining sovereignty over decision-making. The Pharmaceutical Evaluation Report (PER) scheme, the European Union and the Nordic Council on Medicines (Denmark, Finland, Iceland, Norway, Sweden) are examples. This is in no way a loss of sovereignty, but a sharing of expert resources to the advantage of all parties.

WHO encourages regional and international collaboration among DRAs to promote the harmonization of requirements and practices, and to strengthen professional competence. The International Conference of Drug Regulatory Authorities (ICDRA), which was founded for this purpose in 1979, meets biennually in different regions.

It is recommended that DRAs establish communication links with other agencies in order, among other activities, to share scientific reports on new products. Links that include one or more well resourced national authorities are of benefit to less well resourced authorities. As a part of a broader package, such linkages can be of benefit to all participants, for example to take advantage of the larger population base to generate statistics on adverse reactions, drug utilization, and so forth.

However, when sharing scientific reports, it is important to ensure that the data received by both agencies are the same; a report on a different data set will only cause confusion. It is also usual to seek the written agreement of the applicant company before using a report from another DRA. However, this may not be mandatory in all countries, depending on legislation concerning confidentiality of data. If the applicant's approval is not sought, it is nevertheless usual for it to be informed that a foreign report has been used. The usual sequence of events is:

- Make provisional arrangements with the other DRA (e.g. arrange the timing and check whether an evaluation is already available);
- Seek the company's agreement and a statement confirming that the data are the same;
- Exchange the evaluation.

If a report from another DRA is either not relevant (e.g.it relates to a different formulation or different data), is incomplete, or is of a poor scientific standard, the receiving DRA is not obliged to use it and can generate its own report.

Even when a government intends that ultimately the DRA should prepare its own reports, evaluators cannot be expected immediately to acquire the expertise and experience needed; these must be built up over time. The short-term options therefore depend on the expertise and experience that are immediately available. These short-term arrangements should be agreed with government when the marketing authorization activities are still at the planning stage.

N. Collaboration with WHO

Regular publication of marketing authorization decisions is helpful to procurement and distribution networks and to other DRAs. This does not represent a breach of confidentiality as national registers are usually public documents. The *WHO Pharmaceuticals Newsletter* also publishes information on new marketing authorizations, as well as the latest regulatory safety information on, for example, withdrawals and changes in product information. DRAs are encouraged to transmit their regulatory decisions to the Department of Essential Drugs and other Medicines, WHO, 1211 Geneva 27, Switzerland.

WHO distributes an *Alert* to all DRAs when important drug safety problems are detected. The journal *WHO Drug Information* provides more in-depth information, together with a discussion of current topics in drug regulation. The United Nations and WHO jointly prepare a *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments*. This publication enables DRAs which assess applications for marketing authorization to ascertain whether any restrictive action has been taken in other countries. It is updated periodically.

WHO also distributes information to DRAs about new ICH guidelines, both those under discussion and those that have been finalized.

O. Use of external experts as evaluators

Operating activities

While taking maximum advantage of available local expertise, independent experts can be contracted to perform evaluations as consultants to the DRA. Most commonly, the external expert evaluates an application for marketing authorization of a new pharmaceutical product. Experts can also be contracted to conduct other work for a DRA, such as a review of the safety of a particular drug product. External evaluators are of particular value in highly specialized fields such as the pharmaceutical technology of metered-dose aerosols, or clinical specialities such as immunology, neurology and oncology . In countries that use external experts, suitable candidates are usually to be found in universities (e.g. departments of pharmacy, medicine or pharmacology), research institutes and teaching hospitals. Experts in pharmaceutical chemistry and/or the conduct of bioavailability/bioequivalence studies can evaluate applications for marketing authorizations of new multisource products. The reports prepared by these experts should be clearly distinguished from those prepared on behalf of the applicant (e.g. the European Union *expert report*), which do not meet the criterion of regulatory independence. The term *evaluation report* should be used and reserved for reports prepared by or on behalf of a DRA.

Experts may be contracted for a particular evaluation and paid a fee by the DRA, or they may be employees of the government from a different agency, e.g. an institute of health. The cost and benefit of external evaluations must be weighed against the cost of conducting evaluations within the DRA, if the same expertise is available in house. External experts are also useful to extend capacity during periods of high work flow.

It is important for the consultant not to have a conflict of interest, such as a ongoing consultancy with a pharmaceutical company (including the preparation of "expert reports"). Ad hoc contracts with companies, e.g. for the conduct of a particular stability study or clinical trial, are not a bar to performing evaluations provided that the expert declares the contract to the DRA and does not conduct evaluations of the same company's products while the contract is in force. The guidelines on conflict of interest set out in Annex 4 are also applicable to external evaluators. Annex 5 is a model format for a contract with an external evaluator; it includes a declaration concerning conflict of interest.

P. Timeframes for processing of applications

Applications for marketing authorization of new products should be processed within a reasonable time-frame. For all types of product, the DRA must maintain a balance between (1) ensuring that a product is safe, efficacious and of good quality, and (2) not delaying access to the market and availability of the product to the public. It is in the public interest for good new pharmaceutical products to be made available as rapidly as possible, both multisource products and those containing new APIs.

DRAs are encouraged to publish target time-frames.

Q. Publication of marketing authorization decisions

DRAs should publish lists of newly authorized products, including at least the following information:

- Generic name, dosage form, and strength;
- Trade name;
- Marketing authorization holder;
- Product marketing authorization number.

Commercially sensitive confidential details of the marketing authorization, such as routes of synthesis, should not be published except under exceptional circumstances.

If resources permit, DRAs may publish a consolidated list of all products that have received marketing authorization at regular intervals.

IV. REVIEW OF APPLICATIONS FOR MARKETING AUTHORIZATION OF MULTISOURCE (GENERIC) PHARMACEUTICAL PRODUCTS

A. Applicability

The guidelines in this manual are confined to multisource pharmaceutical products containing well established drugs which do not require submission of the complex toxicological and clinical data that accompany new chemical entities. Many of the principles apply to other groups of pharmaceuticals (such as complex biologicals, "alternative" preparations and veterinary medicines) but the details may not. Separate guidelines already exist for herbal medicines (*9*). In many countries regulation of veterinary preparations is undertaken by a different agency.

Details in this manual apply to antibiotics and substances which, although of biological origin, are of low molecular weight and can be isolated as pure substances, such as purified steroids and alkaloids.

On the other hand, the details do not apply to more complex biological substances of higher molecular weight whose purity, potency and composition cannot readily and reliably be determined by chemical or physicochemical analysis. Examples of this group include vaccines, blood products, modified animal tissues, high-molecular-weight hormones, allergens, and the products of genetic engineering or other newer biotechnological techniques.

New licence holders can rarely, if ever, be approved for the second group of biological products only on the basis of *in vitro* comparison with the comparator product. Different brands may
have the same use, for example pertussis vaccine, but each must independently have been shown to be safe and effective. They may even have different dose regimens. Data on plasma concentrations of the "active ingredient" are also usually unhelpful because it is unclear whether precisely the same entity is being measured. These products cannot therefore be approved without safety and efficacy data, and are not the subject of this guideline. The model application form (Annex 6) is not suitable for this group.

WHO is currently developing guidelines on the assessment and marketing authorization of vaccines.

The present guidelines apply to both prescription and non-prescription ("over-the-counter" or OTC) drug products. Products that are authorized for OTC dispensing are assumed to entail lower risk for users than prescription products. Thus, if resources are limited, DRAs may choose to give priority to prescription drug products when committing resources to assess the quality aspects of applications. Control of product information and promotional material, on the other hand, can be equally important for OTC products in order to encourage appropriate use and keep the use of the patient's personal resources for ineffective or less effective

therapy to a minimum.

This manual is not intended to address the question of counterfeit drugs, which is being taken up separately by WHO (*10*). A further manual containing observations and recommendations to combat counterfeit drugs is in preparation (*11*).

B. Initial decisions on options for premarket evaluation

The minimum that must be assured for well established products is:

- Consistent and acceptable quality;
- Interchangeability with pharmaceutical equivalents (Annex 3) on the same market;
- Accurate and locally useful product information.

Together these amount to assurance of quality, safety and efficacy.

In conducting evaluations of well established products, a DRA may:
- Prepare its own reports;
- Rely on *evaluation reports* prepared by other national authorities;
- Rely on *decisions* made by other national authorities;
- Use some permutation of these approaches.

The model application form (see Annex 6) is intended to facilitate data submission, whichever type of evaluation is intended, and should be completed in all cases. A report and/or a decision from another agency may not always be available, particularly for locally developed and manufactured products. In these cases, the DRA must conduct its own evaluation. Similarly, if a WHO-type certificate exists, but does not certify marketing authorization in the issuing country, the DRA must conduct its own evaluation of the data. In these cases, the WHO-type certificate provides information as to regular GMP inspection of the site of manufacture.

> The European Agency for the Evaluation of Medicinal Products (EMEA) issues WHO-type certificates for products that have been authorized via the European centralized procedure. A single such certificate signifies that marketing authorization has been given in all 15 European Union member states .

Each of these options is examined below.

1. *Preparing an evaluation report.* A DRA may prepare its own evaluation report or it may make a commentary on an "expert report" provided by the applicant, if the expert report is of an adequate standard. The evaluation report is needed both for presentation to the expert advisory committee and for future reference in the event of an appeal, subsequent regulatory action or later applications to make changes to the marketing authorization.

The report would normally comprise:
- A brief outline of the data provided in the application;
- The reasons for any disagreement with the applicant's proposals, for example the proposed shelf- life, specifications for the finished product, or the content of product information;
- A summary and evaluation of information on interchangeability, with recommendations and reasons.

If the DRA considers some of the applicant's proposals unacceptable, a letter and/or fax should be sent to the applicant. Such letters are sometimes referred to as a "deficiency notice", "request for additional information" or some similar title. They must be drafted in a manner consistent with legislation.

It is quite legitimate for a DRA to prepare a commentary on an expert report and use the two together as its own evaluation report. The evaluator must remember, however, that his/her function is to provide an independent review of the product and the data. Therefore assertions by the applicant's expert must be checked against the data. If the expert report is of poor quality or does not present a balanced view, the evaluator should not be obliged to use it.

2. *Relying on an evaluation report prepared by another national authority*. If the applicant has confirmed that the data set submitted in the two countries was the same, and with the other authority's evaluation report in hand, the DRA may need only to prepare a "deficiency notice" for return to the applicant (if one is necessary). If certain recommendations made in the other agency's report are considered inappropriate, it is useful to record the reasons, both for future reference and in the event of an appeal.

3. *Relying on a decision made by another national authority*. It is recommended that a WHO-type certificate with approved product information be obtained in all cases, together with an assurance by the applicant that the product to be supplied is identical in all aspects of manufacturing and quality to that in the exporting country. The model application form (see Annex 6) provides for such an assurance. It will also be necessary to consider whether the proposed produce information is appropriate in the importing country. This is further discussed below.

C. Evaluation of data on quality

Irrespective of the extent to which the DRA intends to evaluate the data itself, all the technical data on quality should be provided by the applicant so that, in the event of a reported problem, the batch in question can be fully investigated, for example by quality control laboratory testing. The model application form in Annex 6 requires this information. The types of information in the quality data set that may be needed in the future include:

- Test methodology - for use in testing samples of the product.
- The nature of impurities found in stability studies, and the testing methods for detecting and quantitating them - for use when impurities are found during testing. It is important to know whether impurities are degradation products or contaminants from another source, and if they are present in harmful quantities.

- Sites of manufacture of the active substance or manufacturing intermediates (e.g. granulates) - for use in the event that a particular site is closed because of poor GMP performance.
- Stability data - for comparative purposes when a company wishes to extend the shelf-life of the product.
- Container labelling - for comparative purposes during review by the quality control laboratory.

After a data set on quality has been obtained, the evaluation procedure depends on (1) whether the product is imported or has been locally developed and manufactured, and (2) to what extent the DRA intends to rely on decisions made by other national authorities. Once a DRA has determined whether and under what circumstances it will rely on decisions made by other national authorities, it should proceed in this manner in all but exceptional cases. It is

important that decisions be consistent. An exceptional case might be when an applicant company has previously been found to market substandard products.

The DRA should apply the same standards of quality, safety and efficacy to imported and locally manufactured products.

Domestically manufactured products

If the product has been locally developed and manufactured, the DRA must evaluate the data set itself. It must also ensure that the local site of manufacture has a current manufacturing licence and complies with GMP standards. Testing of a sample in the DRA's quality control laboratory, or in a contract testing laboratory on commission for the DRA, is recommended prior to authorization.

If the product has been developed in another country, for example by a multinational company, but is manufactured locally, a report may be available from the DRA in the other country. The local DRA then has the option of seeking the other country's report, and possibly even relying on the decision made by the foreign DRA, or conducting its own evaluation. However, it is not possible to seek a WHO-type certificate in these circumstances.

Imported products

If the DRA intends to make its own decision, it should first ascertain whether a report is available from another national authority. If it is, the decision on quality can be made quite soon after the report is received. If no other national authority's report is available, the DRA must conduct its own evaluation and then make a decision. In either case, it is recommended that marketing authorizations should not be granted unless a WHO-type certificate is available.

If the WHO-type certificate includes marketing authorization in the exporting country, then the applicant should either provide an assurance that the product to which the certificate applies is identical in all respects to that marketed in the exporting country, or define and justify any differences. The model application form in Annex 6 requires the applicant to provide such an assurance. The influence of climate on stability must also be taken into account, as should local storage conditions, for example the availability of air-conditioned storage or facilities where mean kinetic temperature is monitored (*12)*. If any part of the manufacture is conducted locally (e.g. packaging), the site should have a current licence and be GMP-compliant. Finally,

interchangeability with local pharmaceutical equivalents must be considered (see below), even if the DRA intends to rely on a WHO-type certificate.

Unless either the WHO-type certificate includes marketing authorization in the exporting country, or the differences are minor and are justified, the DRA must conduct its own evaluation of the data, as for locally developed and manufactured products.

WHO-type certificates should normally be accompanied by a copy of the approved product information in the country of origin (section 2A.5 of the model certificate; see Appendix to Annex 2). This should be compared with the product information proposed for local use and evaluated in terms of local applicability, for example in relation to indications.

Information on marketing authorization status in other countries may also provide a degree of

assurance of quality. However, if any reliance is to be placed on marketing authorization status in another country, the applicant should provide an assurance that the batches imported are of at least the same quality and, unless new data are supplied, the same manufacturing origin, including active starting materials. This cannot be assumed. It is recommended that marketing authorizations *not* be granted solely on the basis of marketing authorization in other countries, i.e. without a WHO-type certificate.

Sampling and GMP inspections

Whenever a DRA has relied on decisions made by another national authority or is doubtful about the data provided by the applicant, the product should be sampled and tested in the DRA's quality control laboratory prior to marketing, or in a contract testing laboratory on commission for the DRA.

If manufacture is local, all sites should have a current certificate of GMP. If the DRA is doubtful about the data provided by the applicant, a product-specific GMP inspection should be conducted, supported if necessary by a site inspection.

The recommendations in the above two sections (under "Initial decisions on options for premarket evaluation" and "Evaluation of data on quality" are summarized in the attached decision trees (see chart 1 and 2 on the next two pages).

Chart 1: decision tree for marketing authorizations of ***domestic products***

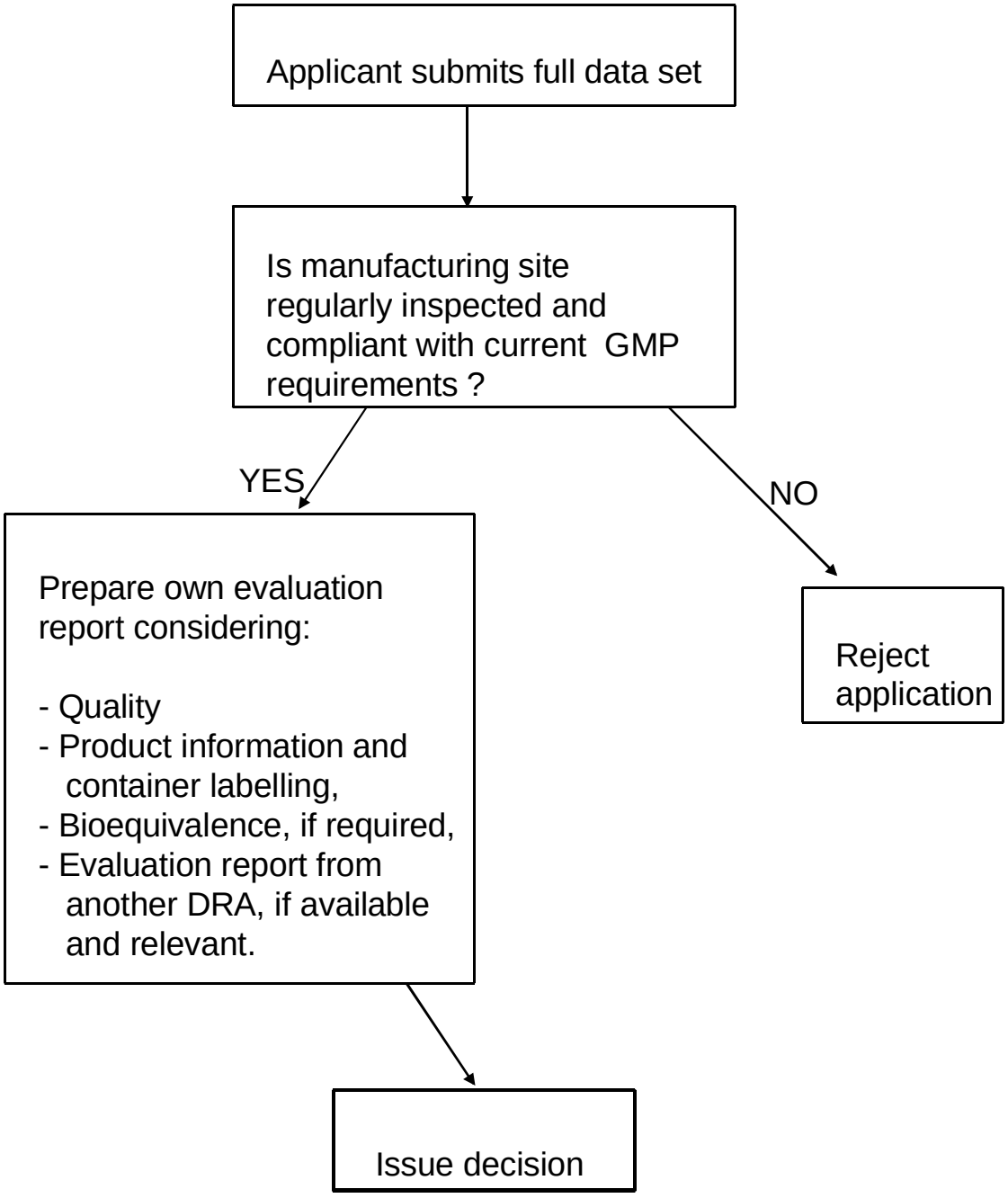
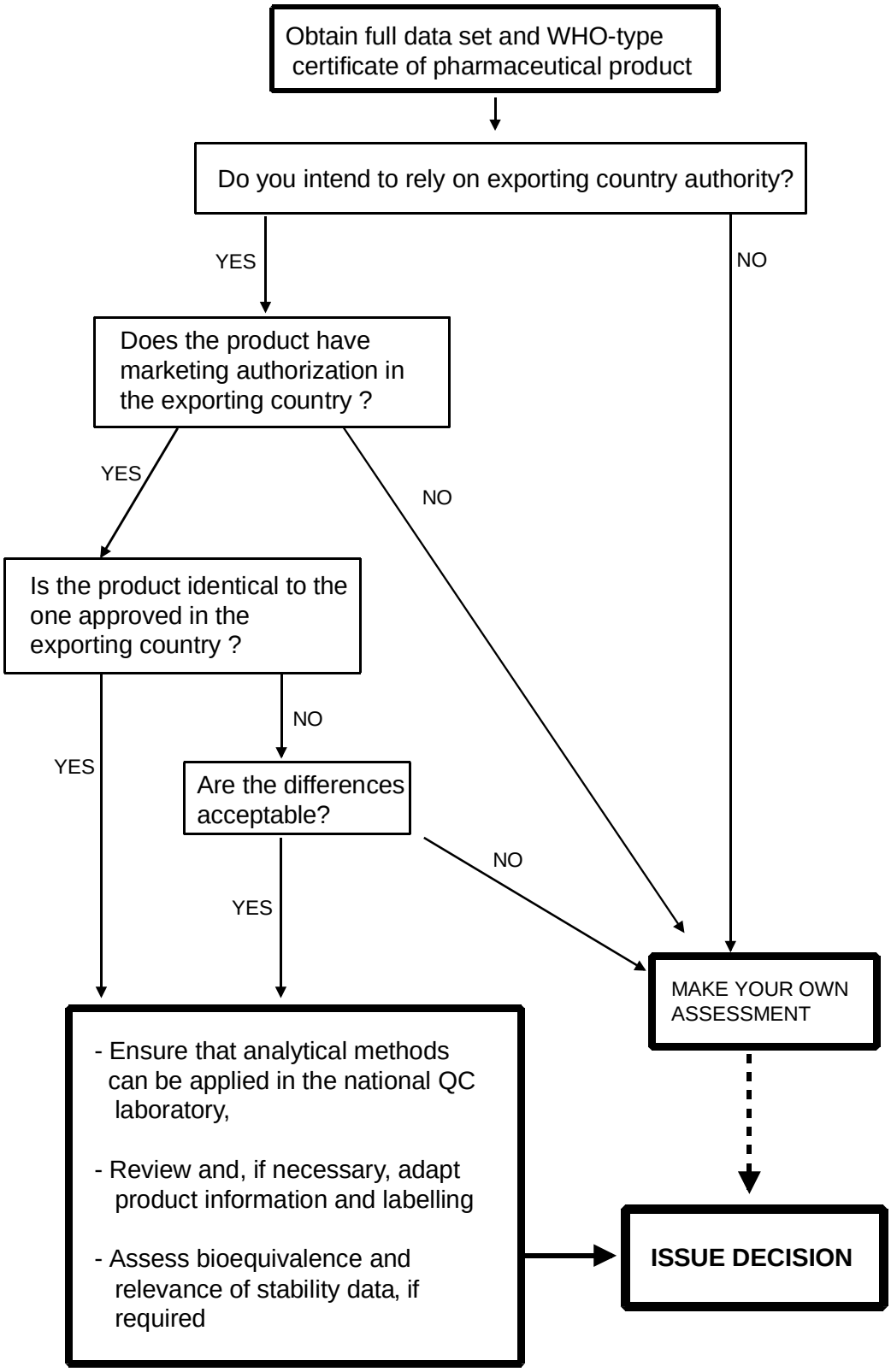


Chart 2: decision tree for marketing authorization of ***imported products***



D. Quality of starting materials

No pharmaceutical product can be of good quality unless it is manufactured from good-quality starting materials. In particular, starting materials should at least comply with the requirements of a current pharmacopoeia if a relevant monograph exists.

Manufacturers of finished products should ensure that each batch of starting materials has been tested for compliance with specifications for identity, strength, purity, and other quality parameters *before* it is used (*13*, p.57). Other quality parameters might include, for example, limits on particle size of an insoluble API, or limits on the viscosity of a solution of an excipient.

In accordance with GMP guidelines (*13*), all shipments should be accompanied by a list of the batch or control numbers, and certificates of analysis for the batch or batches. The WHO GMP guidelines allow reliance to be placed on the supplier's certificate of analysis for the API provided that the manufacturer of the finished product establishes the reliability of the supplier's analysis, normally through periodic validation of the supplier's test results (*13*, p.57). Failure to validate the reliability of suppliers carries a major risk (*10* and *14*). Even when a supplier's findings have been validated, the finished product manufacturer must conduct at least an identity test on every container of starting material.

APIs should where possible be purchased directly from the producer rather than from an intermediary (*13*, p.41). However it is recognized that this is not always possible. It is recommended that each batch of API be tested in full (i.e. not just the identity test) if:

- The batch has been obtained via an intermediary rather than directly from a validated producer, and particularly if the finished product manufacturer is not aware of the identity of the producer; or
- It has not been possible to validate the reliability of the producer's analysis.

Certificates issued by the producer of the API should be retained by the finished product manufacturer for each batch of API. They should be kept for at least the duration of the shelf-life of all batches of finished product in which the batch of API is used.

In the event that a batch of active ingredient is found to be defective, it should be possible to trace all the batches of finished product it has been used to manufacture.

It is recommended that contracts for the supply of starting materials should include a requirement as to quality, for example "...should comply with the current requirements of the International, European, Indian, Japanese or United States Pharmacopoeias". Batches found not to comply should be returned to the supplier.

E. Container labelling

In accordance with GMP guidelines, container labels should comply with national legislation and should include at least the information required by GMP (*13*).

F. Toxicological, pharmacological and clinical data

Full toxicological, pharmacological and clinical data are not usually required in applications for marketing authorization on products containing well established drugs. Exceptions may be made in special circumstances, such as when a new indication or patient population is claimed, use in a new combination is intended, or there is recent evidence that may alter the

accepted view of the drug's safety/efficacy balance. In such circumstances, the DRA can conserve resources by checking whether one of the DRAs with which it has links has already prepared a scientific report on the same data.

New fixed-ratio combination products are regarded as new drugs in their own right. They are acceptable only when (a) the dosage of each ingredient meets the requirements of a defined population group, and (b) the combination has a proven advantage over single compounds administered separately in terms of therapeutic effect, safety or compliance (5, p.6). They should not be treated as generic versions of single-component products.

Where the new product is an alternative brand of an existing product (same active ingredient, dosage form and strength), the data mentioned above are not normally required. However, the applicant should provide, for the information of the DRA, summaries of toxicological, pharmacological and clinical information in the published scientific literature. The summaries should be fully referenced to the scientific literature, and copies of key texts should be provided. The DRA may, in its guidelines as to requirements, opt not to require this information.

Data establishing therapeutic equivalence (see Annex 3) with a suitable locally available pharmaceutical equivalent will usually need to be evaluated.

G. Product Information

The product information is a key document in the regulatory process. It is the means by which the DRA agrees with the company the approved circumstances of use, including indications, patient populations, contraindications, warnings, etc., based on available information on safety and efficacy. It determines how the company may promote the product (see Annex 8), and in large measure it dictates how the product will be used in clinical practice. It is the means of communication between the pharmaceutical company and the health professions, especially the prescriber, and should be a publicly available document. Marketing authorization holders should be encouraged to make product information available on request to enquirers, including patients and health practitioners. It is desirable for DRAs to publish approved product information if resources permit.

Because of its critical role, the product information and its status should be defined in law. For flexibility, the law can lay down a requirement for a document that meets guidelines issued by the DRA. The guidelines can then be updated as the need arises.

The minimum product information provided should be that listed in the sample product information sheet (see Appendix to Annex 8). A copy of the agreed product information should accompany the certificate of marketing authorization when it is despatched by the DRA.

It is not normally acceptable to have two equivalent multisource products on the same market with product information that does not match. In general, one or both sets of the product information will have to be amended so that they are not inconsistent and are as close as possible to each other, although the wording need not be identical. Differences in product information may have to be tolerated in certain situations, particularly where local legislation allows new uses to be patented (new indications in the case of pharmaceuticals) or where market exclusivity arrangements apply. Further comment on the review of product information may be found in Annex 7.
Variations to product information which only add new safety restrictions should be permitted

without prior approval but must be notified to the DRA. The model marketing authorization letter set out in Annex 9 incorporates this provision.

The advice of the expert advisory body is useful in finalizing product information, particularly to take advantage of expertise relating to local circumstances and endemic diseases.

H. Interchangeability

New multisource (generic) pharmaceutical products must be of good quality and at least as safe and efficacious as existing products. The need for interchangeability arises when a patient may change from one brand to another, for example in these circumstances:

- Physicians prescribe by generic name;
- Generic substitution is permitted by national legislation;
- The same brand is not always available, for example in remote areas of the country;
- Patients in hospitals are given whatever brand the hospital has in stock, and sometimes different brands on different occasions;
- Patients receive a different brand after discharge from hospital.

WHO's guidelines on "Multisource (generic) pharmaceutical products" mentions a number of features which are important to interchangeability (see Annex 3, Part one, section 2), and each of these is examined in Annex 7. The science behind demonstrating interchangeability is still evolving; an example is the current debate in the literature on the relevance of "intestinal permeability" (*12*) and how to measure it.

By their nature, different brands of modified (sustained, continuous, prolonged, slow) release products are more likely not to be equivalent than are different brands of immediate, conventional release products. Some DRAs take the view that such products should never be considered interchangeable, while others define a series of studies that should be conducted, including in some circumstances comparative clinical trials. For delayed release products, such as enteric-coated tablets, interchangeability is more readily demonstrated.

V. ISSUE OF WRITTEN MARKETING AUTHORIZATION

To avoid misunderstandings, some form of written marketing authorization should be sent to the applicant when a product is deemed acceptable. A certificate signed by a person authorized by legislation, accompanied by the approved product information, is the usual means of verifying marketing authorization. In the event of a dispute as to whether a product is authorized, possession of a duly signed and dated certificate should be the sole means of proof, unless authorization has subsequently been revoked or has lapsed.

Marketing authorizations usually contain conditions of approval. These may include both standard conditions that apply to all products and specific conditions that apply to the product in question. The standard conditions should be appended to the marketing authorization. Some examples are:

- No changes may be made to pharmaceutical aspects of the product without prior approval, except those listed in [*name of guideline*] as not requiring prior approval.
- The only product information that may be issued with the product is that approved by the DRA, a copy of which is attached to this marketing authorization certificate.
- All promotion must be consistent with the approved product information.

Product-specific conditions might include restriction of the authorization to allow supply only to certain hospitals (e.g. those specializing in selected diseases), or only to certain regions of the country.

Annex 9 contains a model marketing authorization letter to be sent by the DRA to applicants.

VI VARIATIONS

After a product has been authorized for marketing, the manufacturer will often wish to make changes (variations) for a number of reasons. The two common areas for change are pharmaceutical aspects of the product (quality control, manufacturing, shelf-life, etc.) and product information.

Changes should not be discouraged on principle, because they are often intended to improve quality (e.g. stability, batch-to-batch consistency, analytical methodology) or product information (e.g. updates to information on adverse reactions). In an application to vary, the company advises the DRA of an intended change and submits appropriate validation data. To encourage companies to give prior advice of such changes, variations should be processed as quickly as possible. If feasible, the DRA should have a separate unit for processing changes. A balance must be maintained between not placing the company at a disadvantage because it has made the application and yet ensuring that the change has been adequately validated.

Even well resourced agencies find it impossible to evaluate all pharmaceutical changes made to all products. It is necessary, therefore, to define those changes that can be made without the DRA's involvement and those that require prior approval. Some authorities establish an intermediate category of changes which do not require prior approval but which must be notified ("notifiable" changes).

Some DRAs find difficulty in getting the industry to comply with the requirement to apply *in advance* to make pharmaceutical changes. Better compliance can be achieved by these means:

- Definition of minor changes which do not require prior approval or are notifiable;
- A policy that a complete evaluation of the product will *not* be routinely triggered whenever a company applies to make a change (though if an application discloses a major defect, the DRA must take action);
- Where prior approval is required, definition of data requirements in published guidelines so that companies can plan ahead;
- Rapid turn-round of evaluations of applications to make changes;
- Random review, during GMP inspections, of company documentation for consistency with information submitted for marketing authorization purposes;
- A strong and effective system of enforcement of legislation when unauthorized changes are detected.

A model list of variations (changes) that do not need prior approval appears in Annex 10.
Some changes are so major that they constitute a new pharmaceutical product. These should be considered to be an application for a new product and should not be accepted as a variation. Such changes include:

- A change of the API to a different API;
- Inclusion of an additional API, or removal of one API from a multi-component product;
- A change in the dose of one or more of the APIs;

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- A change in dosage form, including:
- Change from an immediate-release product to a slow- or delayed-release dosage form, or vice versa;
- Change from a liquid to a powder for reconstitution, or vice versa;
- Change in the route of administration.

It should be noted that a change in the recommendations for use (e.g. indications or patient population) would make the product *not* interchangeable with other brands and hence would not be acceptable unless the product information of all other brands were changed in the same way. However, as mentioned previously, differences in product information may have to be tolerated where local legislation allows new uses to be patented (e.g. new indications in the case of pharmaceuticals) or where market exclusivity arrangements apply.

VII. PERIODIC REVIEWS

All marketing authorizations should be reviewed at regular intervals. WHO's Guiding Principles for Small National Drug Regulatory Authorities, (*1*) suggests that this should be done every five years. In practice the available resources are likely to dictate the time-frame. Where the authorization is issued for a fixed period, reviews should normally coincide with extensions of its validity. Some countries require more frequent safety updates for products containing new APIs.

DRAs should avoid *routinely* conducting full updates when companies apply to make changes to existing marketing authorizations, because this deters companies from disclosing changes. (But, if an application discloses a major defect, the DRA must take action.) If resources are limited, a better approach is to update products in groups, perhaps beginning with essential drugs.

Candidates for priority might be (though not necessarily in this order):

- Essential drugs;
- Other drugs used to treat life-threatening diseases;
- Drugs for the treatment of endemic diseases;
- Drugs, or groups of drugs, for which there are important new discoveries in safety or efficacy;
- Products with provisional marketing authorization ("grandfathered" - see glossary), about which there is so far no information on file;
- The claims made for OTC products (to minimize expenditure on products which are ineffective for the condition being treated).

Advice on the order of priority to be followed in a given country can be sought from the expert advisory body.

In some countries, *periodic reviews* are explicitly distinguished from marketing authorization *retention fees*. The latter simply involves payment of a charge, usually annually.

The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce includes provision for the issue of a new WHO-type certificate when a periodic review is due (see Annex 2, paragraph 3.5). If a marketing authorization relied in full or in part on a WHO-type certificate, a new certificate should be sought prior to the periodic review.

VIII. SUSPENSION AND REVOCATION OF MARKETING AUTHORIZATION

Marketing authorization may be suspended or revoked, for example in any of the following circumstances:

- The product has proved to be ineffective for the approved indication(s);
- It is strongly suspected that the product is unsafe in the normal conditions of use;
- The quantitative or qualitative composition is not as agreed in the marketing authorization;
- The product is not in compliance with the conditions of marketing authorization;
- The product is being promoted in an inappropriate or unethical manner.

For imported products, if marketing authorization is suspended or withdrawn in a country that supplied a WHO-type certificate, the marketing authorization holder should be asked to state why the authorization should not be suspended. The statement should address the quality, safety and efficacy of the product and GMP certification of the sites of manufacture.

In notifying the marketing authorization holder of any suspension or revocation of marketing authorization, the DRA should state the reasons for the decision and the appeal mechanisms available.

GLOSSARY

The terms listed below are defined specifically for the purposes of this manual. They may be defined differently in other documentation, including annexes in this manual which were, in certain cases, published some years ago.

accountability

Being required to account for one's conduct and actions, usually to an individual or group but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and *transparency* (see below).

active pharmaceutical ingredient (API)

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

advertising

For the purposes of this manual, advertising is considered a part of promotion.

applicant

The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization, or a variation to an existing marketing authorization.

assessment (report)

See *Evaluation Report*

authorization holder

The person or company in whose name the marketing authorization has been granted. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorization holder must be subject to legislation in the country that issued the marketing authorization, which normally means being physically located in the country.

authorized person

A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale. In some other GMP guides and legal texts, the term *qualified person* is used to describe analogous functions.

bioequivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

comparator

In this manual, the term *comparator* is used to mean "the pharmaceutical product with which the new product is intended to be interchangeable in clinical practice". In any particular market, the comparator should be the first in this list that is available.

- the product for which efficacy, safety and quality have been fully established (often the innovator);
- a market leader that has been authorized for marketing after a process of assessment;
- a market leader that is legally marketed but has not been assessed prior to marketing authorization.

See Annex 7, section 16 for guidance on how to deal with the situation where the comparator proves, on testing, to be of poor quality, e.g. it has poor bioavailability.

container labelling

All information that appears on any part of a container, including that on any outer packaging such as a carton.

dosage form

The form of the completed pharmaceutical product, e.g. tablet, capsule, injection, elixir, suppository.

drug

Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

drug master file

A drug master file (DMF) is a master file that provides a full set of data on an API. In some countries, the term may also comprise data on an excipient or a component of a product such as a container.

drug product

See *pharmaceutical product.*

drug regulatory authority

A national body that administers the full spectrum of drug regulatory activities, including at least all of the following functions:

- marketing authorization of new products and variation of existing products;
- quality control laboratory testing;
- adverse drug reaction monitoring;
- provision of drug information and promotion of rational drug use;
- good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations;
- monitoring of drug utilization.

essential drugs

Essential drugs are those that satisfy the health care needs of the majority of the population. As indicated by the Expert Committee on the Use of Essential Drugs (5), each country may generate its own list of essential drugs.

evaluation report

A critical summary and interpretation of the data, with conclusions, *prepared by or on behalf of the drug regulatory authority.*

excipient

Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

expert advisory body

A standing advisory board (or committee) of independent experts, including academic experts and practicing health care professionals.

expert report

In European Union usage critical summary and interpretation of the data, with conclusions, *prepared by or on behalf of an applicant.*

finished product

A product that has undergone all stages of production, including packaging in its final container and labelling.

formulation

The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

generic products

The term *generic product* has somewhat different meanings in different jurisdictions. Use of this term is therefore avoided as much as possible, and the term *multisource pharmaceutical product* (see below) is used instead. Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the innovator products. Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

grandfathered

A product that is grandfathered is one that has been granted marketing authorization because it was already being marketed at the time the marketing authorization system was established.

The terms *provisional registration* or *provisional marketing authorization* (see below) are preferred, but some countries do not have a separate category of provisional marketing authorization.

immediate release dosage form

A dosage form that is intended to release all the active ingredient on administration with no enhanced, delayed or extended release effect.

innovator pharmaceutical product

The innovator pharmaceutical product is generally that which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to requirements at the time of the authorization). When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product.

interchangeability

An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

labelling

The word "labelling" has been avoided in this manual because its meaning is not consistent between Member States. See *container labelling* and *product information.*

licence

See *marketing authorization.*

manufacture (manufacturing)

All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products and the related controls.

marketing authorization

An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, *inter alia*, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform with all the details provided in your application and as modified in subsequent correspondence"). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization.

Once a product has been given marketing authorization, it is included on a list of authorized products - the *register* - and is often said to be "registered" or to "have registration". Market authorization may occasionally also be referred to as a licence or product licence.

master file

A master file is a data set that is:

- submitted by someone other than a finished product applicant, e.g. the supplier of an active ingredient or the supplier of a packaging component;
- a common feature of more than one product, e.g. sterility test procedures; or
- some other matter that is conveniently dealt with by means of a master file.

An applicant for a new marketing authorization or for a variation may make reference to a master file, but must have the permission of the person or company that submitted the master file.

master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including in-process controls.

medicine

See *drug.*

medicinal product

See *pharmaceutical product.*

multisource (generic) pharmaceutical product

Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

new chemical or biological APIs (new APIs)

New chemical or biological APIs are those not previously authorized for marketing for any pharmaceutical use in the country in question. Those provisionally authorized at the time of the initial market inventory are not new pharmaceutical ingredients.

new drug

Any drug that does not match the definition of *well established drug*s (see below).

new pharmaceutical product

A pharmaceutical product that contains a new API, a new combination of marketed APIs, or a new multisource (generic) product. It may be available either on prescription or without prescription.

newer drug

See *new drug*.

periodic review

The regular process, usually occurring every five years, by which the validity of a marketing authorization is renewed and information on a product is reviewed (validated), consolidated and sometimes expanded.

pharmaceutical equivalents

Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance.

pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

product information

A document defining information that may be supplied with or about a pharmaceutical product by or on behalf of the marketing authorization holder. The minimum information in the product information is that defined by WHO's sample product information sheet (see appendix to Annex 8). The content of the product information is agreed between the marketing authorization holder and the DRA at the time the market authorization is issued.

promotion

All informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal products *Ethical criteria for drug promotion,* WHO,1988 (see Annex 8). For the purposes of this manual, promotion includes advertising.

provisional marketing authorization

Temporary authorization following the initial market inventory, and pending full approval based on evaluation of quality, safety and efficacy.

provisional registration

See *provisional marketing authorization.*

quality control

Quality control is concerned with sampling, specifications and testing, and with the organization, documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

register

A list of all the pharmaceutical products authorized for marketing in a particular country. The register is maintained by the drug regulatory authority of the country in question.

registered drug products

Pharmaceutical products that have a marketing authorization.

registration

See *marketing authorization.*

renewal

The word "renewal" has been avoided in this manual because its meaning is not consistent between Member States. See *periodic review* and *retention fee*.

retention fee (for marketing authorization)

A fee paid to maintain marketing authorization, usually annually. Product details are not normally reviewed when retention fees are paid. (See also *periodic review*)

specification - expiry, check or shelf life

The combination of physical, chemical, biological and microbiological test requirements that an active ingredient must meet up to its retest date or a drug product must meet during its shelf-life.

specification - release

The combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

stability

The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. The chemical, physical, microbiological and biopharmaceutical aspects of stability must be considered:

starting material

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

therapeutic equivalence

Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

tracking

Keeping a record of the progress of an application at all stages.

transparency

The term *transparency* means (1) defining policies and procedures in writing and publishing the written documentation, and (2) giving reasons for decisions to the affected party. There is some overlap between *transparency* and *accountability* (see above).

unregistered drug products

Pharmaceutical products that do not have a marketing authorization.

update

See *periodic review.*

Validation

The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Variation

A change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling, and product information.

well-established drugs

APIs (not products) which:

- have been marketed for at least five years in countries that undertake active postmarketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries.

See also *well established drug combinations* and *well established drug products*.

Because this definition refers to active pharmaceutical ingredients and not products, it does not take into account possible sensitivities to excipients and other factors that are relevant to therapeutic equivalence.

well-established drug combinations

Combinations of drugs which:

- have been marketed for at least five years in countries which undertake active postmarketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries.

See also *well established drugs* and *well established drug products*.

Because this definition refers to active pharmaceutical ingredients and not products, it does not take into account possible sensitivities to excipients and other factors that are relevant to therapeutic equivalence.

well-established drug products

Pharmaceutical products which contain well established drugs, and which:

- have been marketed for at least five years in countries that undertake active post-marketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar

indications as in those countries.

WHO-type certificate

A certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (see Annex 2).

ABBREVIATIONS

API	Active pharmaceutical ingredient
ASEAN	Association of South-East Asian Nations
ATC	Anatomic Therapeutic Chemical classification (WHO)
BP	British Pharmacopoeia
CIOMS	Council for International Organizations of Medical Sciences
DDD	defined daily dose
DRA	drug regulatory authority
EFTA	European Free Trade Association
EMEA	European Agency for the Evaluation of Medicinal Products
EP	European Pharmacopoeia
EU	European Union
FDA	United States Food and Drug Administration
GMP	good manufacturing practice
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonisation
INN	International Nonproprietary Name
IP	International Pharmacopoeia
JP	Japanese Pharmacopoeia
MKT	mean kinetic temperature
MPP	multisource pharmaceutical product
OTC	over the counter
PER	Pharmaceutical Evaluation Report scheme (Australia, Austria, Canada, Finland, Germany, Hungary, Iceland, Ireland, Italy, Netherlands, New Zealand, Norway, South Africa, Sweden, Switzerland, United Kingdom)
PI	product information
USP	United States Pharmacopeia

Abbreviations

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ANNEXES

These annexes include certain texts already published by WHO and some new model documents. Material published by WHO is updated from time to time; the most recent version will normally be the most relevant.

Annexes marked with an asterisk are also available in compendium published by WHO in 1997 under the title "*Quality assurance of pharmaceuticals". A compendium of guidelines and related materials*" , Vol. 1.

Annexes

Annex 1: National drug regulatory legislation: guiding principles for small drug regulatory authorities[1]

[1] Also published, with minor editorial changes, as Annex 8 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999 (WHO Technical Report Series, No.885)

1. INTRODUCTION

Countries in both the developed and developing world need to attune their approach to drug regulation to their resources. All share the responsibility of assuring the quality, safety and efficacy of medicinal products including biologicals.

In order to ensure the quality of pharmaceutical products, the manufacture and subsequent handling of the products - including their distribution within the domestic market and their movement in international commerce - must take place under defined conditions and in conformance with prescribed standards. Medicinal products cannot be treated like the generality of consumer commodities. Both legislative and administrative controls must reflect the special considerations to be applied to such products.

Provision of assistance to countries with limited resources has long been regarded as a vital element of the work of the WHO's Division of Drug Management and Policies. In the wake of the 1985 Conference on the Rational Use of Drugs held in Nairobi, WHO embarked on the development of two key documents, namely, the *Guidelines for developing national drug policies (1)* in which legislation and regulation has been identified and described as the first component of a drug policy and a set of *Guiding Principles for Small Drug Regulatory Authorities* which were published in 1990 (2) and endorsed by the World Health Assembly in 1994 (Resolution WHA47.17). Many countries have since begun to implement drug regulatory activities in accordance with these guidelines, but some still need to develop and/or update their basic drug legislation to effectively support drug regulation as stated in these guidelines, i.e.

"Small countries which have yet to introduce comprehensive legal provisions for drug regulation can draw from a diversity of national systems in determining their own requirements. None the less, problems in establishing drug control in developing countries have too often resulted from the adaptation of provisions successful elsewhere but of a complexity that precludes their effective implementation in the country of adoption. It is of paramount importance that legislation and administrative practices are attuned to available resources and that every opportunity is taken to obtain and use information provided by regulatory authorities in other countries".

The manufacture, marketing or importation of medicinal and other health care products continue to be regulated in many countries by statutory texts that are not attuned to prevailing needs or available resources, or by a piecemeal range of independent legal provisions introduced over a period of many years. Even where there is no specific law that relates to medicinal products, there will almost certainly be some legislative provisions that apply to health care products in general. In formulating a new law, therefore, the relevance or implications of existing provisions must be carefully considered. There should be wide consultation with interested parties, particularly those directly concerned with manufacture, importation, distribution and supply of medicinal products.

The present Guidelines with an example of a legislative scheme on medicinal products and accompanying commentaries are destined for drug regulators, legal draughtsmen and parliamentarians in countries wishing to review or elaborate legal texts to regulate medicinal products. The first draft for these Guidelines was developed after an informal consultation on drug legislation for drug regulation by small national drug regulatory authorities, held in Geneva in 1993. The text was subsequently circulated, for consultation and comments, to members of the responsible WHO Expert Advisory Panel, to all WHO Member States through the WHO network of Information Officers and to relevant nongovernmental

organizations, in particular the two nongovernmental organizations representing the pharmacy profession - the International Pharmaceutical Federation (FIP) and the Commonwealth Pharmaceutical Association (CPA). The text was revised and finalized, in the light of comments received, at a further informal consultation that was convened in Geneva in 1996. It should be noted that the example scheme may be closer to the Anglo-Saxon system of legislation and that countries with other cultural and legal backgrounds might consider different approaches, although the overall content of the example would still be relevant.

These guidelines are not intended to be translated as such into national legislations but to be used as source documentation and to be adapted as necessary. While they should be of immediate value to many countries still in the process of establishing drug regulatory and legislative systems, other countries might also profit from such a framework. As regards the latter, it has to be pointed out that authorities should always be cautious about changing systems and procedures that work effectively.

2. DRAFTING NATIONAL LEGISLATION; POINTS FOR CONSIDERATION

These guidelines are based upon and complement the WHO Guiding Principles for Small National Drug Regulatory Authorities (2). They are intended to assist governments in formulating laws and regulations to define and control the national market in medicinal products in the interest of public health. They describe an administrative framework for a regulatory system intended to assure the quality, safety and efficacy of licensed (authorized) medicinal products, and to authorize withdrawal of unsafe and/or illicit medicinal products from the market.

The advice is structured on the assumption that only in exceptional circumstances will a small authority become engaged in full evaluation of all toxicological, pharmacological or clinical properties of a novel medicinal product (for example, a new chemical entity) during the regulatory assessment for marketing authorization. In most instances, the decision will be guided by the regulatory status of the product in the country of origin on the basis of information such as provided through the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (3). However, such approval may depend on a knowledge of, and acceptance of the standards and competence of the drug regulatory authority of the exporting country, by the drug regulatory authority of the importing country.

Objectives

1. To establish a framework for drug regulation through the establishment of a national drug regulatory authority.

2. The primary responsibility of a drug regulatory authority is to operate a system of administration and enforcement intended to ensure that all medicinal products subject to its control conform to acceptable standards of quality, safety and efficacy; the promotion and marketing of medicinal products is in accordance with product information as approved; the use of drugs is rational; and that all personnel, premises and practices employed to manufacture, store, distribute and sell, supply and dispense these products comply with requirements to ensure the continued conformity of the products with these standards up to the time of usage/consumption.

3. These objectives can be effectively achieved only if:

(a) there is in place a mandatory system of licensing/authorizing of:

(i) all medicinal products, whether locally manufactured or imported;

(ii) all local manufacturers, importing and exporting agents, and distributors; and

(iii) all premises and facilities used locally to manufacture, store or distribute medicinal products.

(b) all stages of manufacture and distribution of medicinal products are supervised by appropriately qualified professional staff;

(c) the licensing/authorizing system is complemented by an efficient system of inspection with access to quality control laboratory facilities;

(d) the legislation is enforceable.

4. In addition to providing for licensing/authorizing, a law on medicinal products must also define the terms of reference, powers and functions of the drug regulatory authority; powers of enforcement; and include provision on the right to appeal or otherwise react to the decisions of the drug regulatory authority.

Scope and extent of the legislation[2]

5. The scope of the term "medicinal product" must be defined in all encompassing terms to include, at least, pharmaceutical, biological (vaccines, blood products, other biologicals) and herbal products, including traditional medicines (not harvested by traditional medicine practitioners and sold in package form), products known in many countries as "pharmafoods", "nutriceuticals", or "cosmeceuticals" intended for therapeutic use and whether for animal or human use. The drug regulatory authority must also determine to what extent it intends to exempt related products, such as diagnostic materials, medical devices, cosmetics, health foods and food supplements from its scope of issuing marketing authorizations. It must also be determined in the legislation whether it includes or excludes related products. In borderline cases it might be left to the regulatory authority to decide whether a substance or preparation is considered as a medicinal product.

[2]This text uses the terms both "law" and "legislation". In formulating the legal provisions, it should be noted that certain regulatory matters will be specified in the main statue (enabling or principal law, act or decree) while other matters will be addressed in subsidiary legal texts such as orders, by-laws, regulations and the like.

National drug regulatory legislation

6. The legislation must apply to all institutions and individuals, within both the public and private sectors, that are engaged in, or connected with any aspect of manufacture, promotion, procurement, distribution, or sale or supply of medicinal products.

Terms of reference for the drug regulatory authority

7. The terms of reference, functions, responsibilities, powers and composition of the Authority must be set out in the legislation. The structure, name and style of the Authority will be determined essentially by precedent. In some countries with extremely limited manpower resources, it may be necessary to empower a single individual to function in this capacity. It is particularly important to designate the advisory apparatus and to define the circumstances in which its advice must be obtained.

8. The terms of reference of the Authority need to be clearly set out in the law in a way that establishes its responsibilities with respect to the following functions:

(a) require that all medicinal products manufactured in, imported into (including donations) or exported from the country conform to established criteria of quality, safety and efficacy, and that the personnel, premises and practices employed to manufacture, promote, procure, store, distribute and sell such products comply with defined codes of practice and other requirements;

(b) require continued conformity of medicinal products with such standards until their delivery to the end-user;

(c) require that medicinal products are imported, manufactured, exported, stocked, sold, distributed or otherwise dealt with by duly authorized persons;

(d) grant or refuse, after due assessment, licences/authorizations for medicinal products, whether locally manufactured or imported, and whether destined for the national market or for export;

(e) inspect and license/authorize all domestic manufacturing premises, importing agents, wholesalers, distributors, clinics, hospital dispensaries, retail pharmacies and other outlets where medicinal products are sold;

(f) provide for sampling and analytical and other testing of finished medicinal products released into the distribution chain to assure their compliance with approved specifications;

(g) monitor and review the implementation of the legislation; and

(h) ensure that advertising and marketing is in accordance with product information approved by the drug regulatory authority.

Structure of the drug regulatory authority

9. In order to discharge its duties effectively, the Authority must function within an administrative and legal environment that assures its independence of action and its access to effective channels of communication. Procedures should be laid down by which members and staff of the Authority are appointed, their terms of reference and duration of office. Legislative provisions need to be supplemented or complemented by administrative

procedures designed to safeguard the independence, integrity, effectiveness and impartiality of the Authority. For instance, administrative or disciplinary rules should specify that members and staff should not be involved in any activity that is liable to create a conflict of interest. To maintain the independence of the Authority, responsibilities for regulation of medicinal products should be administratively and operationally separated from activities concerned with their procurement or distribution.

10. The Authority must exercise its powers independently and impartially. Lawful and *bona fide* activities and decisions must be protected by conferring relevant empowerment(s)/immunities on staff and others working for the Authority. Conversely, provision must exist to enable affected parties to obtain relief or redress in accordance with national law. The legislation should contain a clause on the need to ensure the confidentiality of sensitive commercial data.

11. The conditions of service, remuneration and working arrangements must be such that vested interests will not be able to exert any undue influence over staff or others working for the Authority to ensure integrity.

Products, personnel, facilities and practices that are subject to regulation

12. Regulatory controls should extend to all medicinal products on the domestic market as well as those destined for export. As most developing countries rely mainly on imports to meet their drug requirements, it is important not only that the imported medicinal products themselves, but also the procedures involved in promoting, importing, storing, distributing or selling them, are regulated by law. Countries with domestic manufacturing capabilities need to ensure that regulations provide safeguards for the quality of starting materials imported or obtained locally either through a licensing process or as part of Good Manufacturing Practice (GMP).

Issuance of definitive product authorization/licence and transitional provisions

13. In countries without a comprehensive system in place for the regulation of medicinal products, legislation provisions must be formulated for:

- authorizing/licensing of all products proposed for marketing after the "appointed date" for the licensing system;

- transitional arrangements to ensure that products on the market before the appointed date can continue to be marketed, within the regulatory system;

- the subsequent review and full registration of products authorized under the transitional provisions; and

- provision should also be made for regulation of renewal of the product authorization/licence after lapse of period for which the licence is being issued.

Product licensing/issue of marketing authorizations

14. The legislation should establish the legal framework under which applications to market medicinal products are submitted to the drug regulatory agency and the procedure for

the assessment of applications and the grant or refusal of marketing authorizations. The assessment should be based on defined criteria for safety, quality and efficacy. The legislation should place the onus on the applicant to provide information and data necessary for this assessment.

15. The legislation should provide for regulation determining the amount of licensing/authorizing and renewal fees.

Transitional arrangements

16. A procedure is proposed in the WHO Guidelines for Small Drug Regulatory Agencies (1) under which an inventory is drawn up of all medicinal products on the market before the appointed date and the products have the status of being "provisionally authorized/licensed" until such time as full authorizations/licenses are granted. Depending on the timing of the implementation of legislation, in relation to the appointed day, and the availability of information on medicinal products in circulation, the inventory can be established by:

- including requirements, under the legislation, that manufacturers, importers and distributors of medicinal products who intend to continue to manufacture, promote, import, distribute and sell medicinal products after the appointed date must submit specified information on those products to the regulatory authority, before the appointed date;

- compiling the inventory on a more "informal" basis, from available information (price lists, publications, etc.) and data supplied voluntarily by companies.

In either case the information should be collected in a form suitable for entry into a computerized database such as the computerized drug registration system developed within WHO. This will enable the inventory of products to be organized and sorted for subsequent review (see Appendix 2).

Review of provisionally authorized/licensed products

17. The legislation should establish a framework for the review and assessment of provisionally authorized/licensed products for full registration under the product authorization procedures for new products. The timetable for the review should be stipulated by administrative procedures as availability of resources will determine the pace at which these assessments can be undertaken. Priorities for the review of provisionally authorized/licensed products should be determined normally by therapeutic class and based on health-related priorities established within the national drug policy or national health framework/policy.

18. The legal mandate to ask for the submission of application for re-registration of medicinal products marketed prior to the appointed day should be embodied in the legislation but details of the format and content of applications are, again, best dealt with in regulatory guidelines, to allow greater flexibility.

Authorizing/licensing of manufacturers, importers, exporter, distributors and retail outlets

19. Organizations engaged in the manufacture, promotion, importation, exportation, distribution, sale or supply of provisionally registered or licensed medicinal products must

meet prescribed criteria or requirements, regarding facilities, personnel and practices, intended to assure the quality of the product up to the time of usage/consumption. These criteria and requirements must be specified in law. In addition to numerous resolutions of WHO's governing bodies, several texts developed under the aegis of the Organization offer guidance on the elaboration of such criteria and requirements. They are referred to in Appendix 2.

Enforcement

20. The administrative capacity of the Authority must be complemented by an effective inspectorate suitably trained and mandated to monitor compliance with the legislation. To achieve this it is necessary to liaise with other relevant law enforcement offices attached to related government agencies or authorities and in some countries it may also be necessary to enlist the services of other law enforcement officers. In this case, the law must contain suitable provision to confer appropriate authority on such officers to exercise statutory powers under the law governing medicinal products.

21. Provision must exist to handle recalls and destruction of medicinal products from the market requiring manufacturers to recall unsafe, defective or inappropriately labelled products and, when necessary, to suspend manufacture where facilities or operations are found to be below standard, and to cease unethical promotion activities.

22. The emergence in recent years of counterfeit and other illicit products within domestic and international markets has imposed an extra dimension on the work of regulatory authorities and inspectors. It has also created a need for enhanced collaboration between regulatory authorities, licence holders, customs officials and law enforcement authorities, and for greater vigilance by all persons involved with the manufacture, distribution and sale of medicinal products. Consideration should now be given to legal provisions that facilitate timely and efficient exchange of information between concerned parties, both nationally and internationally, inter alia to counteract illicit trade.

Penalties

The law must provide a range of specific penalties and other measures to deter violations of provisions of the legislation. Provisions should be included on the right to appeal, or other measures to react to the decisions of the drug regulatory authority.

Monitoring and Evaluation

23. A legislative text containing the above provisions lays the basis for an important administrative system. It is prudent, therefore, that the text should contain provision for oversight and review of the operation of the system. The Authority should thus have as one of its tasks the preparation of general and thematic reports, at periodic intervals, on the state of implementation of the law. These reports should, *inter alia*, underline deficiencies and weaknesses in the system and propose remedial action. Statutory provision requiring such

reports to be tabled before the legislative assembly will ensure that the relevant reports receive due attention.

3. DEFINING THE SCOPE OF THE MARKETING AUTHORIZATION PROCEDURE FOR MEDICINAL PRODUCTS

National drug regulatory legislation

This section also complements the *WHO Guiding Principles for Small Drug Regulatory Authorities* (1).

The formulation of laws and regulations to define and control the national market in medicinal products is discussed elsewhere. In this section the scope of the application of the authorization/licensing system is discussed with particular reference to finished medicinal products.

The prime objective of every national drug regulatory system is to assure the safety, quality and efficacy of medicinal products. For administrative and judicial purposes a precise definition of "medicinal product" must be established in the national drugs legislation. This definition commonly reflects the usage for which the product is intended e.g., "medicinal purpose" (see item 2.1 above).

In turn, "medicinal purpose" must be defined. Any such definition will refer to the treatment and prevention of disease, but - in order to capture such products as contraceptives and drugs used in anaesthesia - the meaning is commonly extended in a more arbitrary sense to include diagnosis of a disease or a physiological condition, and modification of a physiological function.

Safe and effective use of a medicinal product depends not only upon its innate biological activity, but also upon the judgement, knowledge and qualifications of the person responsible for supplying, selling, prescribing, or administering it and on the evaluation by the national drug regulatory authority. Products have to be classified a.o. subject to international conventions concerning narcotics and psychotropic substances. Furthermore, each medicinal product should be classified as to whether it is:

(a) available only on the authority of a doctor, dentist or veterinary surgeon - prescription only medicines; or

(b) available under the supervision of a pharmacist only from a registered pharmacy - pharmacy only medicines; or

(c) available from retail outlets other than under the supervision of a pharmacist.

The terms of reference of a national drug regulatory authority are typically directed to regulation of the distribution, sale, supply and promotion of medicinal products, not to regulating the practice of medicine. However, decisions taken by the drug regulatory authority will no doubt influence prescribing behaviour and may contribute to rational use of drugs.

The drug legislation should include exemptions from the authorization/licensing provisions, for extemporaneous dispensing and small-scale production carried out by or with the order of appropriately qualified practitioners (pharmacists, physicians, veterinarians and registered practitioners or other named system of medicine). Safeguards should be included in relation to quality assurance and limits on quantities should be included. Special provision is none the less included in many drug acts to provide for regulation of the range of medicinal products that practitioners other than registered practitioners are legitimately allowed to use. Such provisions have been developed in many countries for herbal products and homoeopathic products, in particular.

Every regulatory authority faces the difficulty of determining whether particular "borderline"

products are "medicinal products" within the meaning of the drug legislation. Tonics, food supplements, medicinal soaps and shampoos and other topical preparations for which medicinal therapeutic claims are made are examples of these products. Sufficient flexibility should be preserved in drafting the legislation to enable specific classes of products to be subject to, or to be specifically excluded from the requirement of registration. The DRA may be given statutory power to decide in borderline cases whether a product is a medicinal product or not.

Administrative Coordination

In determining the scope of the marketing authorization, the decisions will be strongly influenced by existing administrative arrangements. It is particularly important to recognize that a department of veterinary services or a department dealing with traditional medicine practices may exert administrative oversight of services without exercising regulatory control over the products used within the specific discipline. Before any decision to extend regulatory oversight to products relevant to these or other departments is contemplated, there is a need for interdepartmental consultation and coordination to determine any required legislative change, with a view to defining the products to be subjected to legal controls, the parameters of the proposed jurisdiction, the required regulatory powers and the associated responsibilities. The mechanics of exercising controls must be discussed and mutually agreed. There must be a clear demarcation of responsibilities and access to effective channels of communication. The administrative and technical competence of the respective ministries, departments, agencies or authorities must be respected at all times; issues of possible duplication or conflict of interest must be clarified at the earliest possible opportunity.

Several legislative and administrative strategies exist to ensure closer and effective coordination between all concerned parties. Provision should be made, for instance, for prior consultation with such parties before the authority considers regulatory action. Representation of such interests on the authority itself is another possible option. The authority may even constitute a sub-committee (e.g. a sub-committee on medical devices) with the mandate of assessing a particular type of product for regulatory action.

Availability of data

For the assessment of certain products, particularly those used in traditional medicine, often only limited data are available. When evaluating such products, etc. great care should be exercised.

The onus is on the applicant to provide the data required by the authority with respect to quality, safety, efficacy and registration status in other countries, for the product for which marketing authorization is requested.

Regulatory agencies may, however, require additional information about ingredients or the availability of similar medicinal products in other countries. Access to published sources of information is needed and authorities may also solicit the cooperation of drug regulatory authorities in other countries willing to share available data, subject to existing rules of confidentiality. WHO also has an important role to play coordinating the supply of information from its own sources and through its network of information officers (see Annex 2).

The revised WHO Certification Scheme on the Quality of Pharmaceutical Products Moving

in International Commerce covers both medicinal products for human use and for use in food-producing animals. Experience to date suggests that its extension to cover a group of veterinary medicines has facilitated the work of authorities. The rationale underlying the Certification Scheme is equally applicable to all health-related products. By legislation the concept of a certificate as provided for by the existing scheme can be extended to cover all or selected health-products.

Technical competence

In view of the technical nature of the work involved in the regulation of medicinal products, the staff of the authority should include appropriately qualified scientific staff. In addition the authority should be able to enlist the assistance of professionals who might have specialist knowledge about some of these products. Through contact with highly evolved authorities, necessary guidance can be obtained to address technical issues which require more detailed expertise. For the purposes of marketing authorizations it is possible for the legislation to provide for the recognition of a medicinal product which possesses a marketing authorization in a named state.

In an increasingly interdependent world, schemes of mutual support and cooperation will provide the basis for establishing systems to assure the quality, safety and efficacy of as many health-related products as possible.

4. EXAMPLE OF A LEGISLATIVE SCHEME FOR REGULATING MEDICINAL PRODUCTS

4.1 General Considerations

The example legislative scheme is structured on the basis of certain assumptions.
Most small developing countries have only a few qualified health professionals and are thus compelled to assign a variety of functions and responsibilities to every available official. This is quite in contrast to the situation in developed countries, and even in developing countries with adequate health manpower, where there is always a group of officials - operating often within a hierarchical structure supported by advisers and committees - entrusted with regulatory responsibilities for different health care products or products with health implications such as drugs, food, devices, herbal medicines, cosmetics, pesticides, chemicals, narcotics, etc.

In the regulatory arena, it is customary to work through institutional mechanisms such as boards, committees or commissions consisting of several professionals. In countries without any regulatory system in place, members of a newly created mechanism will normally have to function almost on a day-to-day basis until most of the preliminary work is completed. With only a handful of qualified health professionals available to attend to all the functions in the Ministry of Health and even in the hospitals, it will be difficult for some of the small developing countries to ensure that such boards or committees will have even a quorum. Even if such boards or committees were to be created, it may well be that one or two officials will have to undertake most of the routine work.

This legislative scheme envisages the establishment of a Drug Regulatory Authority or of a Medicinal Products Board. The latter mechanism is appropriate particularly for those countries which are able to assign a sufficient number of personnel to serve on such a Board. In this event, provision can be made for the appointment of a Secretary to the Board.

The scheme applies only to "medicinal products' (hereinafter referred to as medicinal products or as products). But there is flexibility to extend the scheme to cover other health-related products, if so desired. It may well be that some countries might wish to extend the same (or similar) control regimes as are applicable to medicinal products to other products such as devices, herbal medicines, food and cosmetics, with a few additional provisions and regulation-making powers.

The Drug Regulatory Authority or the Board will be the authority in charge of the day-to-day implementation of the Law. The legislative scheme provides for the creation of a small advisory committee to provide guidance on general or specific policy and other related issues. The nature and composition of the Board and the advisory committee depend essentially on the expertise available in the country and which can be mobilized for the purpose. For this reason, the size, composition and other details are not specified in the scheme itself, but left to be addressed in the regulations.

The control system provided for by the legislative scheme is structured around an "inventory'" of the medicinal products available in the country. Regulation is not possible unless information is available, at some point in time shortly after the law has come into operation, of available products (i.e. imported and/or manufactured).

The first step towards regulation of medicinal products is essentially the compilation of the inventory. Manufacturers and importers can be required, by law, to transmit to the Drug Regulatory Authority or the Board relevant information concerning the products placed on the market on or before a particular date (appointed date) as may be specified in an official publication such as the gazette.

Notification will have the effect of "provisional authorization/registration" for the product. Notified products will be listed in an inventory which will be published or made available for public inspection.

After the appointed date, a medicinal product in respect of which information had not been provided and which does not have the status of being provisionally authorized/registered may not be imported or manufactured without the written permission of the Drug Regulatory Authority or the Board, thus facilitating the exercise of control over the medicinal products currently on the market.

Provisionally authorized/registered medicinal products listed in the inventory will be subjected to a rapid screening process, primarily to secure the withdrawal of those products that do not meet admissible standards of quality, safety and efficacy. The definitive assessment of provisionally authorized/registered medicinal products will have to be planned in accordance with established priorities.

New products (i.e. those not provisionally authorized/registered) may be imported or manufactured only with the prior written permission of the Drug Regulatory Authority or of the Board. Products which are the subject-matter of applications, after the appointed date, for their import or manufacture, will be subjected to technical assessment before a product authorization/licence is granted.

While the proposed legislative scheme is primarily concerned with controls in respect of medicinal products that are being imported or manufactured or sought to be imported or manufactured, the scheme provides for controls in respect of products for export as well.

Modern information technology, using desk-top computers, facilitates the recording, updating and retrieval of information and entries. In the not too distant future it should be possible to access regulatory information provided by selected regulatory authorities and by relevant international organizations such as WHO.

As regulatory decisions affect the interests of parties involved in manufacture, import, export or distribution, the legislative scheme provides for a right of appeal to the Minister or to another Administrative Authority against any decision of the Drug Regulatory Authority or the Board. The Minister or such other Authority may, upon considering the facts of the case, decide to affirm, modify, or rescind the decision of the Drug Regulatory Authority or the Board or to refer it to the Drug Regulatory Authority or the Board for reconsideration. The right of appeal to the Minister or to another Administrative Authority is an administrative safeguard, as an aggrieved person will always have the right to appeal to a court of law, in accordance with the general laws of the country. As the decision of the Minister or of such other Authority will be subject to scrutiny, subject to applicable legal principles, the Minister or the Authority will be expected to bring to bear on the decision an objective and unbiased perspective based on sound policy, scientific knowledge and the particular facts of the case. Courts of law are not normally concerned with technical decisions determined by those with the necessary scientific or technical experience and skills.

Critical to the success of the approach on which this legislative scheme is based is maximum use, through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, of regulatory information in respect of individual medicinal products available through drug regulatory authorities. Regulatory information disseminated by the World Health Organization will also be of particular value in this context (see Appendix 2).

Besides regulating medicinal products, the legislative scheme also provides for regulating - through a auhtorization/licensing system - those who manufacture, import, export, store, dispense or distribute medicinal products. The scheme provides for regulations to be made to specify who may be eligible for authorizations/licences and the procedures for applying for such authorizations/licences.

It is important to note that the legislative scheme contains only the minimum or the basic provisions which a law must contain to provide a sound legislative basis for regulating drugs or medicinal products. In adapting this Law to suit individual needs and circumstances additional provisions may have to be included. The provisions of the legislative scheme will be in addition to those already contained in other legislation dealing with health practitioners, such as medical practitioners and pharmacists, although a chapter on the latter is included.

Due to constitutional or administrative law principles, the laws and regulations of some countries do not necessarily apply to the State or public sector, unless there is specific provision to the contrary. Even if they do apply, sometimes they are not strictly followed to the same extent as by the private sector or the general public. This legislative scheme provides for the State or the public sector to be bound to the same extent as the private sector or the general public. There is no scientific basis to exempt from regulatory and control regimes medicinal products procured or manufactured by or on behalf of the State or the public sector.

POTENTIAL VALUE OF THE SCHEME

The scheme on which the legislative scheme is structured is of particular value to small national drug regulatory authorities with limited manpower and other resources for a number of reasons:

1. The scheme envisages the compilation of an inventory of medicinal products on the market, by placing the burden of providing the necessary information on importers, manufacturers and exporters. After the appointed date, a medicinal product in respect of which the necessary documentation had not been submitted may not be imported, manufactured or exported without the written permission of the Drug Regulatory Authority or the Board, thus facilitating supervision over the movement of medicinal products on the market.

2. The inventory can be compiled by using a small desk-top computer with a software programme tailor made for the purpose.

3. After the appointed date, the Drug Regulatory Authority or the Board can decide on the type of regulatory action to be taken in respect of any individual medicinal product or group of medicinal products by having regard to the country's national drug policy and the health care needs and the nature of regulatory action to which the product is subjected to in other countries that have comprehensive systems in place for the assessment and regulation of medicinal products. The scheme provides for a system of 'provisional authorization/ registration' in respect of medicinal products for which information was provided on or before the appointed date, and for a system of product licensing for medicinal products sought to be imported, manufactured or exported after the appointed date. Provisionally authorized/ registered medicinal products qualify for product licences/marketing authorizations, after evaluation or such products may have to be withdrawn from the market if a decision to this effect is made by the Drug Regulatory Authority or the Board. The process for such evaluation has to be phased in as small national drug regulatory authorities without trained manpower and adequately equipped laboratories will find it difficult to undertake the assessment and registration of drugs, similar to procedures followed in countries where regulatory systems had evolved over many decades and which are able to rely on qualified manpower for the assessment of medicinal products.

4. The scheme has the flexibility to permit provisionally authorized/registered medicinal products to remain on the market until such time that a decision is taken to prohibit or otherwise regulate them, thus preventing any sudden or artificial shortages. This approach has the advantage over those which do not permit any medicinal products to be marketed unless authorized, registered or licensed; constraints of manpower for assessment and authorization will not permit the speedy assessment of medicinal products. Under the scheme the market will be gradually regulated through a process of assessment leading to product registration or withdrawal of the provisionally registered status. As described in section 2.2 of the Guiding Principles for Small National Drug Regulatory Authorities (2) entitled "Screening of provisionally registered products", there must be a rapid initial screening process to secure the withdrawal of products which simply on the basis of a review of their ingredients and indications are judged not to meet admissible standards of safety, quality and efficacy. This must be followed by the phased-in definitive assessment of all provisionally authorized/registered products on the basis of priorities. Applications for products which are to be imported, manufactured or exported for the first time after the appointed date will be assessed simultaneously.

5. In addition to screening individual medicinal products, or groups of medicinal

products, the legislative scheme provides for regulatory action of a general nature. Through regulations or orders provision can be made for compliance with good manufacturing standards; the use of the WHO Certification Scheme on the Quality of Pharmaceuticals Moving in International Commerce; compliance with international nonproprietary names, labelling and advertising requirements etc.

4.2 Model Legislative Text and Commentary

(In the following, text of the commentary is reproduced in italics)

Contents

I. ADMINISTRATION

1. There shall be established a drug regulatory authority which shall comprise of: (i) pharmacists, (ii) physicians (iii) and others.

In order to effectively discharge statutory functions and exercise statutory powers, it is important that the Office of Drug Regulatory Authority should be accorded high visibility within the official structure and be staffed with suitably qualified professions. This includes not only the provision of attractive terms of condition and salary structures, but also access to effective and speedy channels of communication to those in authority, while safeguarding, at all times, the independence of the Office. Under ideal circumstances, the person who functions as the officer of the drug regulatory authority [or the Secretary of the Board] should no longer be involved in drug procurement functions; but where this is not possible, due to manpower constraints, every precaution must be taken to ensure that the two functions of drug regulation and drug procurement are kept distinct and separate.

In the matter of appointing the officer(s) of the drug regulatory authority [or members of the Board] and of the Advisory Committee, one issue which must be addressed is conflict of interest. It is important to ensure that regulatory responsibilities are discharged without fear or favour.

In relation to medicinal products regulation as well as procurement, it needs to be underlined that such products must be considered as a special category; appropriate administrative regulations, including tender or import procedures, must reflect the need to guarantee the independence of those entrusted with regulatory as well as procurement functions.

2. The functions of the drug regulatory authority shall, inter alia, be

(a) to require that all medicinal products manufactured in, imported into or exported from the country conform to prescribed standards of quality, safety and efficacy, and that the personnel, premises and practices employed to manufacture,

promote, procure, store, distribute and sell such products comply with defined codes of practice and other requirements;

(b) to require continued conformity of medicinal products with such standards until their delivery to the end user;

(c) to require that medicinal products are imported, manufactured, exported, stocked, sold, distributed or otherwise dealt with by duly authorized persons;

(d) to grant, after due assessment, authorizations/licences for medicinal products, whether locally manufactured or imported, and whether destined for the national market or export;

(e) to cancel the authorization/registration of, or cause to be recalled from the market, such medicinal products, the continued use of which may be detrimental to public health;

(f) to maintain an inventory of provisionally authorized/registered medicinal products;

(g) to publish lists of provisionally authorized/registered medicinal products and of products with marketing authorizations from time to time for public information;

(h) to ensure that dossiers for marketing authorizaton of medicinal products are kept up to date by the applicants and to approve alterations/changes thereto;

(i) to inspect and license/authorize all manufacturing premises, importing agents, wholesalers, distributors, hospital dispensaries, pharmacies and retail outlets;

(j) to provide for sampling and analytical and other testing of finished medicinal products released into the distribution chain to assure their compliance with labelled specifications;

(k) to monitor the market for the presence of illegal/counterfeit medicinal products;

(l) to ensure that the promotion and marketing of medicinal products is in accordance with product information as approved by the drug regulatory authority;

(m) to approve the use of unregistered/unauthorized medicinal products for clinical trial purposes or for compassionate use and to regulate clinical trials on medicinal products;

(n) to disseminate information on medicinal products to the health professions in order to promote their rational use;

(o) to accumulate authorization/registration and application and renewal fees;

(p) to monitor and review the implementation of the legislation;

(q) to advise the Minister on matters concerning control and authorization/registration of medicinal products;

(r) to amend the rules and regulations as deemed necessary to keep pace with

time demand(s).

This section lists some of the more important functions of the drug regulatory authority. Additional functions can be added to this catalogue.

3. The drug regulatory authority shall appoint such other officers as may be necessary to assist the Drug Regulatory Authority (Board) to perform duties and to exercise powers under this Law. Such officers shall be known as "authorized officers".

For purposes of inspection, supervision and monitoring, the drug regulatory authority [or Board] will need the assistance of other officers. The number and type of officers needed depend essentially on the profile of the pharmaceutical industry. However, it is important that the manpower needs for implementing the Law are duly taken into consideration in the health manpower planning process.

4. The Minister shall, in consultation with the drug regulatory authority appoint a Medicinal Products Advisory Committee to advise the drug regulatory authority on any general matter concerning the implementation of the technical aspects of the Law or with regard to any specific medicinal product.

It is envisaged that the Committee will provide guidance on technical/scientific as well as administrative matters. As there are significant differences, even in small countries, in the availability of pharmacologists, medical practitioners, and pharmacists who can be considered for appointment to a Committee of this nature, the legislative scheme does not address issues such as composition, size, quorum, working procedures and other aspects. Committee members should be free from conflict of interest. These are matters to be regulated by way of regulations promulgated under the Law. The drug regulatory authority should be an ex-officio member; ideally, such an officer should serve as the secretary of the Committee as well.

II. PROVISIONAL REGISTRATION/MARKETING AUTHORIZATION AND INVENTORY OF MEDICINAL PRODUCTS

5. (1) The drug regulatory authority shall, by order published in the gazette [variant: or through other means of notification], require manufacturers, importers and exporters of medicinal products to notify the drug regulatory authority such particulars as are specified in the order concerning the medicinal products which such manufacturers, importers, or exporters wish to continue to manufacture, import, export or sell after such date (hereinafter referred to as the appointed date) as is specified in the order.

(2) Medicinal products in respect of which a notification has been received by the drug regulatory authority on or before the appointed date shall be listed in the provisionally authorized/registered medicinal products inventory (hereinafter referred to as the inventory) and until granted a product licence/marketing authorization or ordered by the Drug Regulatory Authority (Board) not to be manufactured, imported, exported or sold such products shall have the status of provisionally authorized/registered medicinal products.

(3) After the appointed date no person shall import, manufacture, export or sell a medicinal product not listed in the inventory without the prior written permission of the drug regulatory authority unless a product authorization/licence has been granted in respect of such product under section 6 of this Law.

(4) The inventory, the format of which may be laid down in regulations, shall be made available for inspection at such place and at such times as specified by the drug regulatory authority in an order published in the gazette or one or more newspapers as may be specified in the regulations.

(5) The inventory shall be revised accordingly as and when provisionally authorized/registered products listed therein have been granted a product authorization/licence under section 6 (1) or the drug regulatory authority has ordered under section 6 (3) that any such provisionally authorized/registered medicinal product should not be manufactured, imported, exported or sold from such date as is specified in the order.

This section provides for a system of provisional authorization/registration for medicinal products which are being manufactured, imported, exported or sold as of a specific date, and which will be continued to be manufactured, imported, exported or sold even after that date (appointed date).

Medicinal products which are notified on or before the appointed date will be listed in a provisionally authorized/registered medicinal products inventory. The scheme envisages this inventory as well as a register. The latter is for medicinal products which have been granted a product licence/marketing authorization. The procedure for screening provisionally authorized/registered products as well as new applications for other medicinal products is contained in section 6.

In respect of a provisionally authorized/registered medicinal product, the drug regulatory authority may decide one of two things: either to grant a product licence/marketing authorization or to phase out or ban its manufacture, import, sale or export. In either event, the product will be deleted from the inventory. If a product licence/marketing authorization is granted, it will be entered in the register of medicinal products for which a product licence/marketing authorization has been granted (see section 9).

At some point of time - depending on the pace at which the screening process can proceed - the inventory will cease to exist, as all products which had the provisionally authorized/registered status would have been screened and either granted a product licence/marketing authorization or eliminated from the market.

Section 14 makes it an offence to manufacture, import, sell or export a product unless it has a marketing authorization or is deemed to be provisionally authorized/registered.

A renewal process will be adapted at regular intervals for those products which show satisfactory performance in the market and comply duly with regulation.

III. SCREENING OF PRODUCTS AND ISSUANCE OF PRODUCT LICENCES/ AUTHORIZATIONS

6. (1) In accordance with the national drug policy and the country's health-care needs, and in relation to considerations of product quality, safety and efficacy, the drug regulatory authority shall make an order as to whether a provisionally authorized/registered product or a product which is not listed in the inventory but in respect of which an application

for its manufacture, import, export or sale has been filed after the appointed date, should be granted a product licence/marketing authorization.

(2) The drug regulatory authority may at any time call upon any manufacturer, importer or exporter to furnish such information as is required in order to enable a provisionally authorized/registered product or a product sought to be manufactured, imported or exported after the appointed date, to be evaluated and assessed.

(3) The drug regulatory authority may at anytime, after scientific evaluation, determine that an authorized/registered product should not be eligible for a product authorization/licence and that such product should not be manufactured, imported, sold or exported either with immediate effect or from such date as is specified in an order made by the drug regulatory authority.

(4) Upon an order made under subsection 1 or 3 taking effect, the inventory shall be accordingly revised with respect to the entry in relation to the relevant product.

This section deals with the factors to be taken into account in screening medicinal products (either those which are provisionally authorized/registered or in respect of which a new application has been made for manufacture, import, export or sale) and the procedures to be followed. in granting a product licence/marketing authorization.

7. Any manufacturer, importer or exporter who fails, without valid reason, to furnish such particulars within the stipulated time-limit, or within an extended time-limit as may have been granted by the drug regulatory authority, shall not be entitled to manufacture, import, sell or export such medicinal product from such date as is specified by the drug regulatory authority in a communication addressed to such manufacturer, importer or exporter.

This section addresses the situation where a manufacturer, importer or exporter has defaulted in submitting the necessary particulars and data to enable the product to be screened.

8. In determining whether a product licence/marketing authorization should be granted or not, the drug regulatory authority shall consult the Medicinal Products Advisory Committee, relevant authorities and health professionals and may take into account regulatory information from other countries and relevant international organizations.

This section addresses the consultative process that must take place when products are being screened.

The drug regulatory authority may wish to consider how a particular medicinal product has been regulated in other countries. Product licences/marketing authorizations may be subject to various terms and conditions relating to

- *manufacture;*
- *importation;*
- *exportation;*
- *marketing;*
- *distribution;*
- *prescribing;*
- *use;*

National drug regulatory legislation

- *labelling;*
- *packaging;*
- *pricing;*
- *advertising/promotion; or*
- *conditions of sale.*

The legislative scheme is structured on the basis that drug regulatory authorities in small countries should make the maximum use of regulatory information available in the public domain. Such information is available through a number of sources such as the WHO Certification Scheme on the Quality of Pharmaceuticals Moving in International Commerce (the WHO Certification Scheme); the authorities of countries with advanced drug regulatory systems; the World Health Organization; and drug-related commercial as well as non-commercial publications (e.g. national formularies; drug compendia; medical journals).

Appendix 2 describes the various publications and services that have been developed specifically to support drug regulatory authorities.

9. The drug regulatory authority shall maintain a register of medicinal products for which marketing authorizations have been issued and shall make the register, or extracts from it, available at such place and at such times as specified by the drug regulatory authority in an order published in the gazette or one or more newspapers as may be specified in the regulations.

This section provides for a register of medicinal products for which product licences/marketing authorizations have been granted to be maintained. This register will eventually replace the inventory as all provisionally authorized/registered products would have to be screened.

10. Regulations made under this Law shall specify the terms, conditions, and validity of product licences/marketing authorizations, the format of the register, and the particulars to be furnished to obtain a product licence/marketing authorization for provisionally approved/authorized products or for products not listed in the inventory, and other requirements, including the payment of fees, for applications for a product licence/marketing authorization.

This section provides for regulations to be made on matters relating to licences/marketing authorizations and the register. The use of modern technology such as computers facilitates the compilation, updating and printing of the inventory and the register. WHO's Division of Drug Management and Policies has developed a Model package for computer-assisted drug registration which can be adapted for purposes of developing such inventories or registers and even for issuing of licences/marketing authorizations (see Appendix 2).

11. (1) The drug regulatory authority may revoke or suspend the marketing authorization for importation, manufacture, sale or exportation of a medicinal product if it appears or there is reason to suspect that the conditions for the license are no longer fulfilled.

(2) The drug regulatory authority may vary the provisions of the marketing authorization provided it is satisfied that such a variation does not adversely effect the safety, quality or efficacy of the medicinal product.

(3) The order of the drug regulatory authority may specify how the order is to take effect, particularly with regard to recalling the product from the market, and the procedures, if any, for notifying health professionals and the public.

(4) An applicant (licence/marketing authorization holder) shall not deviate from the particulars submitted in the drug registration dossier, unless authorized thereto by the drug regulatory authority. A formulation or other error pertaining to a medicine shall be immediately reported to the drug regulatory authority. An adverse drug event reported to a licence/marketing authorization holder shall be conveyed to the drug regulatory authority by the license holder within three days of the initial report.

This section empowers the regulatory authority to take prompt action to withdraw a product from the market when such a course of action is warranted by public health considerations.

12. (1) Any manufacturer, importer or exporter who is aggrieved by an order made by the drug regulatory authority under this Part may appeal to the Minister [variant: Authority], in writing, within two weeks from the date of the order.

(2) On receipt of an appeal the Minister [variant: Authority] may decide whether or not the drug regulatory authority should be directed to rescind, suspend, vary, modify, reconfirm or reconsider the order in respect of which the appeal has been lodged.

This section provides for administrative relief, prior to institution of action in a court of law in accordance with the country's legal and judicial system. Provision for administrative relief in the first instance is an important remedy, as litigation generally tends to be protracted, costly and inconvenient to all parties concerned.

IV. OTHER ACTIVITIES REQUIRING AUTHORIZATION/LICENSING

13. (1) On or after such date as is specified in a notice published in the gazette or in any official publication as may be specified in the regulation a person carrying on a business of manufacturing, importing, exporting, compounding, storing, dispensing, selling, supplying or otherwise distributing medicinal products must possess a valid authorization/licence in order to carry out that activity.

(2) The Licensing Authority shall maintain a register of pharmacies.

An application for registration of pharmacy premises under this section must be made in accordance with Regulations issued by the Minister.

(3) The particulars to be furnished by applicants for an authorization/licence, their qualifications and suitability, and the terms, requirements and conditions subject to which such authorizations/licences may be granted shall be specified by the drug regulatory

authority in regulations made under the Law.

(4) Any person aggrieved by a decision of the drug regulatory authority may appeal, within two weeks of the notification of the decision of the drug regulatory authority, to the drug regulatory authority.

(5) On receipt of an appeal the drug regulatory authority may decide whether or not the drug regulatory authority should be directed to rescind, suspend, vary, modify, reconfirm or reconsider the order in respect of which the appeal has been lodged.

Parts II and III were concerned with medicinal products, whereas this Part IV deals with persons-individuals, companies, firms, hospital clinics or dispensaries, pharmacies etc.- who need a licence/authorization to engage in various activities.

There is a right of appeal to the Minister or to another administrative authority against any decision of the drug regulatory authority. Provision for administrative relief in the first instance is an important remedy, as litigation generally tends to be protracted, costly and inconvenient for all parties concerned.

V. GENERAL PROVISIONS

14. It shall be an offence under this Law for any person to manufacture, import, sell or export a product after the appointed date unless such product at the time of manufacture, import, distribution or export has the status of a provisionally authorized/registered medicinal product under section 5(2) or has received a product licence/marketing authorization under section 6.

This section deals with the situation when a product which is neither provisionally authorized/registered nor covered by a product licence/marketing authorization is manufactured, imported, distributed, sold or exported after the appointed date.

15. After such date as is specified under section 13(1) of the Law, it shall be an offence for any person to engage in any of the activities mentioned in that section, unless such person holds a valid authorization/licence granted by the drug regulatory authority or is otherwise legally entitled to engage in any such activity.

This section deals with the situation when a person engages in an activity mentioned in section 13 without a licence or legal right (under another law).

16. No person shall manufacture, import, export, compound, store, sell, promote or distribute a medicinal product

(a) that is unfit for use in humans or in animals;
(b) that is adulterated;
(c) that has upon it any natural or added deleterious substance which renders it injurious to health;

(d) that has been manufactured, prepared, preserved, packaged or stored for sale under insanitary and/or unfavourable conditions; or
(e) that has been labelled, packaged or promoted in a manner that is false, misleading, deceptive or likely to create an erroneous impression regarding its

source, character, value, quality, composition, potency, merit or safety;

(f) no person shall manufacture, import, export, distribute, sell, supply or use any counterfeit starting materials;

(g) no person shall manufacture a medicinal product using any counterfeit starting materials or without taking reasonable measures to ensure that the starting materials used or employed in the manufacture of such medicinal products are not counterfeit or of suspect quality;

(h) no manufacturer, importer, exporter, distributor, pharmacist, health practitioner, health worker or other person shall manufacture, import, export, compound, prepare, promote, sell, supply, obtain, display, dispense or otherwise distribute, for a fee or by way of sample or gift any medicinal product which is a counterfeit or known or suspected to be a counterfeit.

This section is of a general nature aimed at ensuring that only medicinal products which meet acceptable standards are marketed.

One potential problem area in implementing this provision is the lack of quality control facilities in small developing countries where products could be tested and verified. Through cooperative arrangements with neighbouring countries with good quality control facilities it should however be possible to get products tested in such facilities. Participation in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce also provides an opportunity for quality defects to be investigated.

17. Where any standard is prescribed for any medicinal product, no person shall label, package, sell, offer for sale, distribute or promote any such medicinal product which does not conform to such standard in such manner as is likely to be mistaken for the medicinal product for which the standard has been prescribed.

The applicable standards will have to be specified in the regulations.

18. (1) The drug regulatory authority or any authorized officer shall have the power to visit and inspect any manufacturing plant, processing unit, business establishment, warehouse, office or any premises used for or in connection with the manufacture, import, export, distribution, storage, sale, supply, dispensing or use of any medicinal product, to take samples of any medicinal product or of any substance, and to examine records or other documents relating to any medicinal product.

(2) No person shall refuse to permit the drug regulatory authority or any authorized officer to enter and inspect or take samples or documents.

(3) An inspector may at any reasonable time and on production of his/her certificate of authority enter any premises:-

(a) for the purpose of ascertaining whether there is or has been any convention of the legislation;

(b) generally for the purpose of discharging his/her functions under the legislation.

(4) An inspector may:

(a) inspect the premises, any article and any document for the purposes of the legislation;

(b) seize any substance, article or document which he/she has reasonable cause to believe to be a substance, article or document in which or by means of which an offence under the legislation is being or has been committed.

"Premises" for the purposes of this section includes any premises, ship, aircraft or vehicle. "Premises" does not include a dwelling house.

It will be useful to develop a plan of action, with appropriate checklists and guide, to enable authorized officers to conduct inspections.

19. Any person who contravenes or fails to comply with any provision of this Law or any regulation or any order made under this Law shall be guilty of an offence, and on conviction shall be liable to a fine between .....and ..... or imprisonment for a term not exceeding ..... months/years, or both; in the case of a continuing offence, to a fine not exceeding ..... for every day or part of a day during which the offence has continued.

The minimum and maximum penalties (imprisonment and/or fine) must be determined having regard to the penalties generally prescribed by other laws currently in force in the country.

The need for "deterrent penalties" must be carefully balanced with the risk of "over-kill". Too high a penalty, particularly one entailing mandatory jail sentences, for instance, can lead to lax enforcement and will be counter-productive in the longer run. On the other hand, products like medicinal products need to be manufactured and handled with great care and circumspection; any deliberate or negligent departure from established standards and norms can result in mortality and morbidity, otherwise avoidable. The ubiquitous problem with counterfeit drugs has reinforced the need for severe penalties for certain types of violations involving deliberate or fraudulent behaviour.

20. The provisions of this Law shall extend to all persons, both public and private sector engaged in manufacturing, importing, exporting, compounding, storing, distributing, promoting, selling or in any other way dealing with medicinal products.

In some countries express statutory provision is required for a law to apply to the State or to the public (government) sector. It is important that regulatory controls apply to all medicinal products, irrespective of who is responsible for their manufacture, import or export, distribution or sale.

21. Regulations shall be made for all or any of the matters for which the Law provides for regulations to be made and, in particular, for the following purposes:

(a) Prohibiting, limiting, restricting, or imposing conditions on, either generally or in relation to (i) a particular medicinal product, (ii) manufacture, importation, exportation, compounding, dispensing, administration, sale or supply of medicinal products; (iii) printed packaging material, package leaflets and data sheets/product information, promotion to health professionals, advertising to the general public and conduct of marketing practices.

(b) Withdrawing medicinal products from sale or *distribution.*

(c) Prescribing the standards to be followed in the manufacture, storage, sale,

supply, dispensing and distribution of medicinal products.

(d) Classifying medicinal products for purposes of regulating importation, manufacture, compounding, prescribing, dispensing, selling, storage and distribution.

(e) Regulating persons entitled to import, manufacture, compound, export, store, prescribe, dispense or sell medicinal products.

(f) Prescribing the terms, conditions, procedures and time-limit for the issuance of licences/authorizations under Parts III and IV of the Law and the forms, fees, particulars and records necessary in connection with applications for licensing and grounds for suspension, cancellation or withdrawal of licences/product authorizations.

(g) On the composition and terms of reference of the Medicinal Products Advisory Committee [Variant: and of the Board of Medicinal Products].

(h) Granting exemptions from the requirement of a product licence/marketing authorization for imports of medicinal products required for a named patient or to meet a public health emergency.

(i) Designating laboratories and analysts for the purposes of conducting analyses and submitting reports.

(j) Regulating the licensing/authorizing and licensing/authorization renewal fees in order to support the drug regulatory functions.

(k) Prescribe any regulation in matters pertaining to this Act.

(l) Regulating clinical trials on medicinal products.

(m) Regulating drug donations.

(n) Regulating obligation to report on drug adverse reactions.

(o) Obligation to report on product variations such as quality or manufacturing change.

There are a number of sections which provide for regulations to be made. This catalogue is in addition to the matters referred to in those sections.

VI. INTERPRETATION

22. The Legislation should include an interpretation of terms which may be used in a special context. In this model text given here, terms which might need interpretation include:

"Appointed date" means the date specified under section 5 (1) of the Law;

"Inventory" refers to the listing of provisionally registered/authorized medicinal products under section 5 (2) of the Law;

"Medicinal product" means any medicine intended for human or veterinary use, presented in its finished dosage form or as a starting material for use in such dosage form;

"Minister" means the Minister responsible for matters relating to medicinal products;

"Person" includes a natural person as well as a body corporate, partnership or association of persons, and establishments such as hospital pharmacies, clinics, and health centres storing or distributing medicinal products;

"Provisionally authorized/registered" is used in relation to a medicinal product which has been listed in the inventory under section 5 of the Law and which has not been screened for purposes of a product licence/marketing authorization under sections 6 and 9 of the Law;

"Register" means the register of medicinal products for which a product licence/marketing authorizaton has been issued in terms of sections 6 and 9 of the Law or the register of persons, i.e. the pharmacist and pharmacy assistant;

"Sell" means to sell for cash or on credit or by way of exchange and whether by wholesale or retail and "sale" shall have a corresponding meaning.

The above are some of the more important terms used in the legislative scheme which need to be defined. But other terms can also be defined. The WHO text on Good Manufacturing Practices for Pharmaceutical Products contains a number of definitions of terms such as "manufacture" which can be included, after adaptation, if necessary, in the definition section.

Appendix 1. Registration of pharmacy personnel

In order to assist countries to up date existing laws or to draft new ones, this document offers an example for a legislative scheme on registration of pharmacy personnel. The text and included provisions should be adapted to suit national conditions, requirements and situations.

(1) No person shall practise as a pharmacist unless his/her name has been registered as a pharmacist by the Licensing Authority by virtue of this Act/Law.

(2) An applicant for registration as a pharmacist must:

(a) hold a pharmaceutical qualification granted by a university, or institution of equivalent standing; and

(b) have practised the pharmaceutical profession for a period of not less than [two] years; and

(c) be in good health and have no adverse police record; and

(d) fluently speak and read [the national language and/or others]; and

(e) pass such an examination as the Minister may consider necessary.

(3) (1) Except as is provided by this Act/Law, no person other than a person registered as a pharmacist shall:

(a) conduct and administer a registered pharmacy;

(b) in the course of any trade or business prepare, mix, compound or dispense any medicinal product or poison except under the supervision of a pharmacist;

(c) assume, take, exhibit or, in any way make use of, any title, emblem, description or addition reasonably calculated to suggested that he/she is registered as a pharmacist.

(2) For the purpose of subsection (1)(c) of this section the use of the word "pharmacist" or "chemist" or "druggist" or any similar word or combination of words shall be deemed to suggest that the owner of the business on those premises is, or purports to be, a registered pharmacist.

(4) No person shall practise as a pharmaceutical technician [an assistant in pharmacy] unless he/she has obtained registration as a pharmaceutical technician [assistant in pharmacy] by the Licensing Authority by virtue of this Act/Law.

(5) An applicant for registration as a pharmaceutical technician [assistant in pharmacy] must:

(a) hold a recognized certificate as a pharmaceutical technician [assistant in pharmacy]; and

(b) have practised within the pharmaceutical profession for a period of not less than [two] years in a pharmacy under the supervision of a pharmacist; and

(c) be in good health and have no adverse police record; and

(d) fluently speak and read [the national language and/or others]; and

(e) pass such an examination as the Minister may consider necessary.

(6) The applications for registration under sections 2 and 5 of this Act/Law must be made in accordance with regulation issued by the Minister.

(7) The Licensing Authority shall maintain a register of pharmacists and technicians [assistants in pharmacy].

(8) A pharmacist and technician [assistant in pharmacy] must perform his/her duties in accordance with the ethics of the pharmaceutical profession and in particular must:

(a) at all times act in the interest of the patient;

(b) uphold the honour and dignity of the pharmaceutical profession and not bring the profession into disrepute;

(c) at all times have regard to the laws and regulations applying to medicinal products, pharmaceutical practice and maintain a high standard of professional conduct;

(d) respect the confidentiality of information acquired in the course of his/her professional practice;

(e) offer services to the public in premises which reflect the professional nature of pharmacy.

(9) The Minister shall by Regulation establish a Pharmaceutical Practice Committee comprising;

(i) a pharmacist Chairman appointed by the Minister; plus

(ii) [three] registered pharmacists; and

(iii) [two] registered technicians [assistants in pharmacy];

(iv) [one] lay member.

(10) The Pharmaceutical Committee shall:

(i) advise the Minister on any matter relating to the pharmaceutical profession and the practice of pharmacy;

(ii) ensure the maintenance of high standards of practice and conduct among pharmacists and technicians [assistants in pharmacy] and to promulgate codes of conduct;

(iii) set standards of education and training, where appropriate, for pharmacists and/or technicians.

(2) The Pharmaceutical Committee may regulate its own procedure.

(11) (1) The Minister shall by Regulation establish a Disciplinary Committee to inquire into the conduct of a registered pharmacist or registered technician [assistant in pharmacy] whom it is alleged has been convicted of a criminal offence or is in breach of any of the provisions of section 8 of this Act/Law.

(2) The Disciplinary Committee shall comprise of:

(i) a [Legal] Chairman appointed by the Minister; plus

(ii) two registered pharmacists; and

(iii) one registered technician [assistant in pharmacy].

(iv) No member of the Pharmaceutical Committee shall be a member of the Disciplinary Committee.

(3) The Disciplinary Committee shall, after inquiry, have power:

(i) to issue a reprimand/warning to a registered pharmacist or registered technician[assistant in pharmacy]; or

(ii) to adjourn an inquiry with conditions; or

(iii) to recommend to the Minister that the name of a registered pharmacist or registered technician [assistant in pharmacy] be suspended or removed from the respective register;

(iv) to regulate its own procedure.

(13) The Minister, by Regulation, may fix fees for the initial registration of pharmacists, technicians [assistants in pharmacy] and pharmacies. Annual fees may also be payable to retain the names of pharmacists, technicians [assistants in pharmacy] and pharmacies on the respective registers.

(14) Any person who contravenes section 1, 3 or 4 of this Act/Law shall be guilty of an offence and liable to a fine not exceeding .....

Appendix 2. Guidelines, documents and other regulatory instruments established by WHO to support drug regulatory authorities

Over the years WHO has issued many technical and administrative guidance publications that bear direct relevance to drug regulation, such as:

Guiding Principles for Small National Drug Regulatory Authorities (2)*

WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (3)

Guidelines on import procedures for pharmaceutical products (3)

Multi-source pharmaceutical products: WHO guideline on registration requirements to establish interchangeability (3)

Provisional guidelines on inspection of pharmaceutical manufacturers (4)

Good manufacturing practices for pharmaceutical products (GMP) (4)

Good manufacturing practices for biological products (5)

Guidelines for the assessment of herbal medicines (3)

Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology (4)

Guidelines for good clinical practice for trials on pharmaceutical products (GCP) (6)

Use and protection of recommended international nonproprietary names for pharmaceutical substances (7)

WHO guideline on stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms (3)

Regulation and licensing of biological products in countries with newly developing regulatory authority (2)

Ethical criteria for medicinal drug promotion (8)

Model List of Essential Drugs and Sixth Report of the WHO Expert Committee on the Use of Essential Drugs (9)

* See section on References and Selected Bibliography

WHO also fosters exchange of information among drug regulatory authorities and the

following four WHO publications are particularly helpful for world-wide regulatory information. The WHO *Pharmaceuticals Newsletter*, published monthly, contains notifications received from WHO Member States on the regulation of human and veterinary drugs and medical devices, and also provides information on the surveillance of marketed products. The quarterly, *WHO Drug Information*, contains a section on 'Regulatory Matters' dealing with individual drugs subjected to regulatory action. Another quarterly, *International Digest of Health Legislation*, reproduces important regulatory texts adopted by WHO Member States and geo-political groupings such as the EEC. The *Essential Drugs Monitor* reports on current developments and new publications. The *Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments* published annually by the United Nations is another good source of information. As the 'Introduction' to the 1991 List states: "It constitutes a tool which helps Governments to keep up-to-date with regulatory decisions taken by other Governments and assists them in considering the scope for eventual regulatory action. It enables government agencies which review applications for product registration to ascertain easily restrictive regulatory decisions made in other countries. It complements and consolidates the information produced within the United Nations system, including the World Health Organization's quarterly bulletin WHO Drug Information and its Pharmaceutical Newsletter..." (p. v). Countries with developed systems of drug registration or with similar social and health-care structures can be requested to provide information as to the availability of certain drugs on their markets, and the terms and conditions subject to which such drugs are being imported, manufactured, marketed or exported.

The revised *WHO Certification Scheme on the Quality of Pharmaceuticals Moving in International Commerce* enables importing countries to request the following types of documents which will provide more information with regard to any product in the country of export:

- Certificate of a Pharmaceutical Product;
- Statement of Licensing Status of Pharmaceutical Product;
- Batch Certificate

The Product Certificate requires essentially the following information to be furnished by the designated regulatory authority in the country of export:

- the proprietary name (if applicable) and dosage form;
- active ingredient(s) per unit dose (together with a qualitative listing of other ingredients contained in the dosage form);
- particulars of product licence and of product licence holder (or particulars of applicant for certificate if the product is not licensed to be placed on the market for use in the country of export);
- if the product is not licensed to be placed on the market for use in the country of export, the reason why such authorization is lacking (not required/not requested/under consideration/refused);
- particulars concerning inspection of the manufacturing plant in which the dosage form is produced; and
- approved product information and technical summary.

The Statement of Licensing Status, on the other hand, indicates only whether or not the products listed in the certificate are licensed to be placed on the market for use in the country of export. This Statement is essentially intended for use by importing agents who are

required to screen bids made in response to international tenders.
Upon request, WHO assists countries with a standardized approach to the computerization of drug regulatory data, for example, processing marketing authorizations and maintaining product lists. Under preparaton are modules on: monitoring of imporations/exportations and reporting on psychotropic and narcotic drugs and information handling in a drug quality control laboratory.

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Annex 2: *Guidelines for Implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce[1]

1. Provisions and objectives

[1] Also published, with minor editorial changes, as Annex 10 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863)

1.1 A comprehensive system of quality assurance must be founded on a reliable system of licensing[1] and independent analysis of the finished product, as well as upon assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as “good manufacturing practices” (GMP).

1.2 In 1969, the Twenty-second World Health Assembly, by resolution WHA22.50, endorsed requirements for Good Practices in the Manufacture and Quality Control of Drugs *(1)* (referred to henceforth as "GMP as recommended by WHO"). These comprise internationally recognized and respected standards that all Member States are urged to adopt and to apply. These requirements have since been revised twice. The first revision was adopted by the Health Assembly in 1975 in resolution WHA28.65 (2). A second revision of the requirements is included in the Thirty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Products *(3)*.

1.3 These standards are fully consonant with those operative within the countries participating in the Convention for the Mutual Recognition of Inspection in Respect of the Manufacture of Pharmaceutical Products, and other major industrialized countries. They also provide the basis for the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (referred to henceforth as "the Scheme") recommended initially in resolution WHA22.50 *(1)*. The Scheme is an administrative instrument that requires each participating Member State, upon application by a commercially interested party, to attest to the competent authority of another participating Member State that:

- a specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;

- the plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO; and

- all submitted product information, including labelling, is currently authorized in the certifying country.

1.4 The Scheme, as subsequently amended in 1975 *(2)* and 1988 *(4)*, by resolutions WHA28.65 and WHA41.18, is applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals.

1.5 Provision for certification of active ingredients is also included within the scope of the Scheme. This will be the subject of separate guidelines and certificates.

2. Eligibility for participation

2.1 Any Member State intending to participate in the Scheme may do so by notifying the Director-General of the World Health Organization, in writing, of:

- its willingness to participate in the Scheme;

[1] Throughout this document licensing refers to any statutory system of approval required at national level as a precondition for placing a pharmaceutical product on the market.

- any significant reservations it intends to observe relating to this participation; and

- the name and address of its national drug regulatory authority or other competent authority.

2.2 These notifications will be subsequently announced in the monthly *WHO Pharmaceutical Newsletter*. An updated consolidated list will be published annually in the *Newsletter* and will be available to governments at other times from: the Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland. (*See also section 3.3*)

2.3 A Member State may opt to participate solely to control the *import* of pharmaceutical products and active substances. This intention should be stated explicitly in its notification to the World Health Organization.

2.4 A Member State intending to use the Scheme to support the *export* of pharmaceutical products should first satisfy itself that it possesses:

an effective national licensing system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;

GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;

effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country, including access to an independent quality control laboratory;

a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and the legal
power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;

administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.

2.5 Each Member State assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision, under any circumstance, for external inspection or assessment, either of a competent national authority or of a manufacturing facility. However, should a Member State so wish, it could approach WHO, or a well-recognized Drug Regulatory Authority, to occasionally delegate consultants to act as advisors in the course of national inspections, and inspector training activities.

3. Requesting a certificate

3.1 Three documents can be requested within the scope of the scheme:

- a Certificate of a Pharmaceutical Product (*Product certificate)*

- a Statement of Licensing Status of Pharmaceutical Product(s) and

- a Batch Certificate of a Pharmaceutical Product.

3.2 Proposed formats for these documents are provided in Annexes 1, 2 and 3 of these guidelines. To facilitate their use, these documents are presented in forms suitable for generation by computer. All participating countries are henceforth urged to adopt these formats to facilitate interpretation of certified information. Requests for the provision of certificates offering more limited attestations — for instance, that the manufacturer complies with GMP or that the product is authorized for "free sale" within the country of export — are discouraged. Similarly, requests should not be made for certification of information going beyond the scope of this Scheme. When manufacture takes place in a country other than that from which the product certificate is issued, an attestation relevant to compliance of the manufacture with GMP may still be provided (as an attachment to the product certificate) on the basis of inspections undertaken for registration purposes.

The Explanatory Notes attached to the three documents referred to above are very important. Whilst they are not part of the document to be certified, they should always be attached to the certificate.

3.3 A list of addresses of competent national regulatory authorities participating in the Scheme that are responsible for the registration of pharmaceutical and/or veterinary products, together with details of any reservations they have declared regarding their participation in the Scheme may be obtained from WHO as indicated in section 2.2.

3.4 The competent authority in each country participating in the Scheme should issue guidelines to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the drug regulatory process and the circumstances in which each of the three types of documents will be required.

Certificate of a Pharmaceutical Product

3.5 The Certificate of a Pharmaceutical Product (Appendix 1) issued by the exporting country, is intended for use by the competent authority within an importing country in two situations:

- when the product in question is under consideration for a product licence that will authorize its importation and sale;

- when administrative action is required to renew, extend, vary or review such a licence.

3.6 All requests for certificates should be channelled through the agent in the importing country *(see section 3.4)* and the product licence holder or other commercially-interested party in the exporting country ("the applicant"). The applicant should submit the following information for each product to the authority issuing the certificate:

- name and dosage form of product
- name and amount of active ingredient(s) per unit dose (International Nonproprietary Name(s) where such exist(s)),

- name and address of product licence holder and/or manufacturing facility,
- formula (complete composition including all excipients; also particularly when no product licence exists or when the formulation differs from that of the licensed product),
- product information for health professionals and for the public (patient information leaflets) as approved in the exporting country,

For product information to be attached to the certificate see item 4.7

3.7 The certificate is a confidential document. As such, it can be issued by the competent authority in the exporting country ("the certifying authority") only with the permission of the applicant and, if different, of the product-licence holder.

3.8 The certificate is intended to be incorporated into a product-licence application in the importing country. Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

3.9 When any doubt arises about the status or validity of a certificate, the competent authority in the importing country should request a copy directly from the certifying authority, as provided for under section 4.9 of these guidelines.

3.10 In the absence of any specific agreement, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.

3.11 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.

3.12 Supplementary attestations are obtainable only at the discretion of the certifying authority and with the permission of the applicant. The certifying authority is under no obligation to supply additional information. Requests for supplementary information should consequently be referred to the applicant, and only in exceptional circumstances to the certifying authority.

Statement of Licensing Status

3.13 Statement of Licensing Status (Appendix 2). This attests only that a licence has been issued for a specified product, or products, for use in the exporting country. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and preparation of information. The importation of any product that is provisionally selected through this procedure should be determined on the basis of a Certificate of a Pharmaceutical Product.

Batch certificate

3.14 A Batch certificate of a Pharmaceutical Product (Appemdix 3) refers to an individual batch of a pharmaceutical product and is a vital instrument in drug procurement. The provision of a Batch certificate is usually a mandatory element in tender and procurement documents.

A Batch certificate is normally issued by the manufacturer and only *exceptionally,* as in the case of vaccines, sera and some other biological products, by the competent authority

of the exporting country. The Batch Certificate is intended to accompany and provide an attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already been licensed in the importing country. The Batch Certificate should include the specifications of the final product at the time of batch release and the results of a full analysis undertaken on the batch in question. In most circumstances these certificates are issued by the manufacturer to the importing agent (i.e. the product licence holder in the importing country), but they must be made available at the request of — or in the course of any inspection made on behalf of — the competent national authority.

4. Issuing a certificate

4.1 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO emblem, but a statement should always be included to confirm whether or not the document is issued in the format recommended by WHO.

4.2 When the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:

(a) applies identical GMP standards to the production of *all* batches of pharmaceutical products manufactured within the facility, *including those destined exclusively for export*.

(b) consents, in the event of identification of a quality defect consonant with the criteria set out in section 5.1, to relevant inspection reports being released, in confidence, to the competent authority in the country of import, should the latter so require.

4.3 When the applicant is not the manufacturer of the finished dosage form, the certifying authority should similarly satisfy itself – in so far as it has authority to inspect the records and relevant activities of the applicant – that it has the applicant's consent to release relevant reports on the same basis as described in section 4.2 (b) above.

4.4 GMP as recommended by WHO assigns to the manufacturer of the finished dosage form responsibility for assuring the quality of active ingredients. National regulations may require that suppliers of active ingredients be identified in the product licence, but the competent authority may have no power to inspect them.

4.5 Notwithstanding this situation, a certifying authority may agree, on a discretionary and voluntary basis, and at the request of a manufacturer, to undertake an inspection of a manufacturer of active ingredients to satisfy specific requirements of a requesting authority. Alternatively, pending the development of specific guidelines for active pharmaceutical ingredients, the certifying authority may be able to attest that the manufacturer is an established supplier of the substance in question to manufacturers of finished dosage forms licensed for marketing under its jurisdiction.

4.6 Whenever a product is purchased through a broker or another intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the product for which the applicant is not directly responsible have been undertaken in compliance with GMP as recommended by WHO.

4.7 The certifying authority should officially stamp and date all copies of product information submitted to it in support of an application for a certificate and intended to be appended to the certificate. Every effort should be made to ensure that certificates and all annexed documentation are consonant with the version of the product licence operative on the date of issue. When available, the certifying authority will add a Summary Basis of Approval or any other material the authority deems relevant. Translation by an applicant of these materials into a widely used language, preferably English, shall be deemed to satisfy the provision of 3.10.

4.8 Any additional attachment to a certificate submitted by the applicant, such as price lists of products for which bids are offered, should be clearly identified as not comprising part of the attestation made by the certifying authority.

4.9 To avert potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous and to enable the certifying authority to maintain comprehensive records of countries to which specific products have been exported, each certificate should identify the importing country and be stamped on each page with the official seal of the certifying authority. If requested, an identical copy, clearly marked as duplicate, should be forwarded by the certifying authority on demand directly to the importing country authority.

5. Notifying and investigating a quality defect

5.1 Each certifying authority undertakes to institute enquiries into any quality defect reported in a product exported in accordance with the provisions of the Scheme, on the understanding that:

- the complaint is transmitted, together with the relevant facts, through the competent authority in the importing country;

- the complaint is considered to be of a serious nature by the latter authority; and

- the defect, if it appeared after delivery of the product into the importing country, is not attributable to local conditions.

5.2 In the case of obvious doubt, a participating national authority may request WHO to assist in identifying an independent quality control laboratory to carry out tests for the purposes of quality control.

5.3 Each certifying authority undertakes to inform WHO and, as far as is possible, all competent national authorities, of any serious hazard newly associated with a product exported under the provisions of the Scheme or of any criminal abuse of the Scheme directed, in particular, to the export of falsely labelled, spurious, counterfeited or substandard pharmaceutical products. On receipt of such notification, WHO will transmit the message immediately to the competent national authority in each Member State.

5.4 WHO stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

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Appendix 1

Model Certificate of a Pharmaceutical Product

Certificate of a Pharmaceutical Product[1]

This certificate conforms to the format recommended by the World Health Organization. (general instructions and explanatory notes attached)

No. of Certificate:

Exporting (certifying) country:

Importing (requesting) country:

1. Name and dosage form of product:

1.1 Active ingredient(s)[2] and amount(s) per unit dose[3].

For complete composition including excipients see attached[4].

1.2 Is this product licensed to be placed on the market for use in the exporting country?[5] yes/no *(key in as appropriate)*

1.3 Is this product actually on the market in the exporting country? yes/no/unknown (*key in as appropriate)*

If the answer to 1.2 is yes, continue with section 2A and omit section 2B;
If the answer to 1.2 is no, omit section 2A and continue with section 2B.[6]

2A.1 Number of product licence[7] and date of issue:

2A.2 Product-licence holder (name and address):

2A.3 Status of product licence holder[8] : a/ b/ c/ *(key in appropriate category as defined in note 8)*

2A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form is:[9]

2A.4 Is summary basis of approval appended?[10] yes/no (*key in as appropriate*)

2A.5 Is the attached, officially approved product information complete and consonant with the licence? [11] yes/no/not provided *(key in as appropriate)*

2A.6 Applicant for certificate, if different from licence holder (name and address)[12]:

2B.1 Applicant for certificate (name and address):

2B.2 Status of applicant: a / b / c / *(key in appropriate category as defined in footnote 8)*

2B.2.1 or categories b and c the name and address of the manufacturer producing the dosage form is:[9]

2B.3 Why is marketing authorization lacking?
not required/not requested/under consideration/refused
(key in as appropriate)

2B.4 Remarks[13] :

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?
yes/no/not applicable[14] *(key in as appropriate)*

If no, or not applicable proceed to question 4

3.1 Periodicity of routine inspections (years):

3.2 Has the manufacture of this type of dosage form been inspected?
yes/no *(key in as appropriate)*

3.3. Do the facilities and operations conform to GMP as recommended by the World Health Organization?[15]
yes/no/not applicable[14] *(key in as appropriate)*

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product[16].
yes/no *(key in as appropriate)*

If no, explain:

Address of certifying authority:

Telephone no:. . . . . Fax number:

Name of authorized person:

Signature:

Stamp and date:

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

1 This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2 Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

3 The formula (complete composition) of the dosage form should be given on the certificate or be appended.

4 Details of quantitative composition are preferred but their provision is subject to the agreement of the product-licence holder.

5 When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.

6 Sections 2A and 2B are mutually exclusive.

7 Indicate, when applicable, if the licence is provisional, or the product has not yet been approved.

8 Specify whether the person responsible for placing the product on the market:

(a) manufactures the dosage form;
(b) packages and/or labels a dosage form manufactured by an independent company; or
(c) is involved in none of the above.

9 This information can only be provided with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence has to be updated or it is no longer valid.

10 This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

11 This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC)

12 In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission has to be provided to the authority by the applicant.

[13] Please indicate the reason that the applicant has provided for not requesting registration.

(a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;
(b) the product has been reformulated with a view to improving its stability under tropical conditions;
(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
(e) any other reason, please specify.

[14] Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

[16] This section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

The layout for this Model Certificate is available on diskette in Word Perfect from the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Appendix 2

Model Statement of Licensing Status of Pharmaceutical Product(s)

No. of Statement.....

Exporting (certifying) country:
Importing (requesting) country:

Statement of Licensing Status of Pharmaceutical Product(s)[1]

This statement indicates **only** whether or not the following products are licensed to be put on the market in the exporting country.

Applicant (name/address):

Name of product	**Dosage form**	**Active ingredient(s)**[2] **and amount(s) per unit dose:**	**Product-licence No. and date of issue**[3]

The certifying authority undertakes to provide, at the request of the applicant (or, if different, the product-licence holder)**,** a separate and complete Certificate of a Pharmaceutical Product in the format recommended by WHO, for each of the products listed above.

Address of certifying authority:

Name of authorized person:

Telephone/fax numbers:

Signature:
Stamp and date:

This statement conforms to the format recommended by the World Health Organization *(general instructions and explanatory notes below)*

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

[1] This statement is intended for use by importing agents who are required to screen bids made in response to an international tender and should be requested by the agent as a condition of bidding. The statement indicates that the listed products are authorized to be placed on the market for use in the exporting country. A Certificate of a Pharmaceutical Product in the format recommended by WHO will be provided, at the request of the applicant and, if different, the product-licence holder, for each of the listed products.

[2] Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

[3] If no product licence has been granted, enter "not required", "not requested", "under consideration" or "refused" as appropriate.

The layout for this Model Statement is available on diskette in Word Perfect from the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Appendix 3

Model Batch Certificate of a Pharmaceutical Product

Manufacturers/Official[1] Batch Certificate of a Pharmaceutical Product

This certificate conforms to the format recommended by the World Health Organization *(general instructions and explanatory notes attached)*

1. No. of Certificate:

2. Importing (requesting) authority:

3. Name of product

3.1. Dosage form

3.2 Active ingredient(s)[2] and amount(s) per unit dose:

3.2.1 Is the composition of the product identical to that registered in the country of export?yes/no/not applicable[3] (*key in as appropriate*)

If no: please attach formula (including excipients) of both products.

4. Product-licence holder[4] (name and address):

4.1 Product-licence number[4]:

4.2 Date of issue[4]:

4.3 Product licence issued by[4]:

4.4 Product certificate number[4,5] :

5.1 Batch number: . . . . . .

5.2 Date of manufacture:

5.3 Shelf life (years): . . . . . .

5.4 Contents of container:

5.5 Nature of primary container:

5.6 Nature of secondary container/wrapping:

5.7 Specific storage conditions:

5.8 Temperature range:

6 Remarks[6]:

7. Quality analysis:

7.1 What specifications apply to this dosage form. Either specify the pharmacopoeia or append company specifications.[7]

7.1.1 In the case of a product registered in the exporting country, have these company specifications[7] been accepted by the competent authority? yes/no
(key in as appropriate)

7.2 Does the batch comply with all parts of the above specifications?
yes / no *(key in as appropriate)*

7.3 Append certificate of analysis[8]

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person:

Telephone no:. . . . . Fax number:

Signature of authorized person:

Stamp and date:

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

These forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

Certification of individual batches of a pharmaceutical product is only undertaken exceptionally by the competent authority of the exporting country. Even then, it is rarely applied other than to vaccines, sera and biologicals. For other products, the responsibility for any requirement to provide batch certificates rests with the product-licence holder in the exporting country. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the competent authority in the exporting country. A copy should be sent to the product- licence holder.

[1] Strike out whichever does not apply.

[2] Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

[3] "Not applicable" means that the product is not registered in the country of export.

[4] All items under 4 refer to the product licence or the Certificate of a Pharmaceutical Product issued in the exporting country.

[5] This refers to the Certificate of a Pharmaceutical Product as recommended by the World Health Organization.

[6] Indicate any special storage conditions recommended for the product as supplied.

[7] For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.

[8] Identify and explain any discrepancies from specifications. Government batch release certificates issued by certain governmental authorities for specific biological products provide additional confirmation that a given batch has been released, without necessarily giving the results of testing. The latter are contained in the manufacturer's certificate of analysis.

The layout for this Model Certificate is available on diskette in Word Perfect from the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Appendix 4
Glossary and index

In order to facilitate understanding, this glossary explains terms in the Guidelines and/or refers to relevant sections. It is considered as supplementary information and not as being a formal part of the Scheme.

For clarity, all definitions that have been taken from the glossary of "Good manufacturing practices for pharmaceutical products" (*1*) are preceded by an asterisk.

abuse of Scheme
See item 4.9 and 5.2 of the guidelines

active ingredients
See item l.5, 4.4 and 4.5 of the guidelines

addresses of competent authorities
See item 2.2 and 3.3 of the guidelines

applicant
The party applying for a *Product Certificate*. This is normally the product licence holder. In all instances, having regard to commercial confidentiality of certain data, the competent authority in the exporting country must obtain permission to release these data from the product licence holder, or, in the absence of a product licence, from the manufacturer.

authentication of certificates
See item 4.9 of the guidelines

**batch* (or lot)
A defined quantity of a starting material, packaging material, or product processed in a single process or series of processes so that it can be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

batch certificate
A document containing information, as set out in Annex 3 of the *Guidelines* for use, will normally be issued for each batch by the manufacturer. Furthermore, exceptionally a batch certificate may be validated or issued by the Competent authority of the exporting country, particularly for vaccines, sera and other biological products. The batch certificate travels with every major consignment (see also section 3.14 of the guidelines).

**batch number*
A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, and the certificates of analysis, etc.

**bulk product*
A product that has completed all processing stages up to, but not including, final packaging.

certifying authority
This is the *competent authority* that issues product certificates. It shall ensure that it possesses the capacities listed in item 2.4 of the *Guidelines.*

charges for product certificates
See item 3.11 of the guidelines.

competent authority
The national authority as identified in the formal letter of acceptance in which each Member State informs WHO of its intention to participate in the Scheme. The extent of its participation should be indicated in the letter of acceptance (see item 2.1 of the guidelines). The competent authority can issue or receive certificates.

WHO makes available upon request a continuously updated list of addresses of competent authorities and, when applicable, the specific conditions for participation.

competence and evaluation of national authority
See item 2.4, 2.5 and 4.2 of the guidelines.

dosage form
The form of the completed pharmaceutical preparation, e.g. tablet, capsule, elixir, suppository.

drug regulatory authority
An authority appointed by the government of a Member State to administer the granting of Marketing Authorizations for pharmaceutical products in that country.

**finished product*
A product that has undergone all stages of production, including packaging in its final container and labelling.

free sale certificate
See item 3.2 of the guidelines.

GMP certificate
See item 3.2 of the guidelines.

importing agents, guidelines for
See item 3.4 of the guidelines.

language of product certificates
See item 3.10 of the guidelines.

licence holder
An individual or a corporate entity being in the possession of a marketing authorization of a pharmaceutical product.

licensee
An individual, or corporate entity responsible for the information and publicity on, and the pharmacovigilance and surveillance of batches of, a pharmaceutical product and, if applicable,

for their withdrawal, whether or not that individual or corporate entity is the holder of the marketing authorization.

limits of certification by competent authority
See item 3.12 and 4.8 of the guidelines.

lot
See batch.)

**Manufacture*
All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products, and related controls.

**Manufacturer*
A company that carries out at least one step of manufacture. (For the different categories of manufacturer see Appendix 1, explanatory note No. 7)

Marketing authorization
See product licence.)

pharmaceutical product
Any medicine intended for human use or administered to food-producing animals, presented in its finished dosage form or as an active ingredient for use in such dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

product
See pharmaceutical product.)

product certificate
A document containing the information as set out in Appendix 1 of the guidelines that is validated and issued for a specific product by the competent authority of the exporting country and intended for use by the competent authority in the importing country or - in the absence of such an authority - by the drug procurement authority. (see also item 3.5 of the guidelines).

Transmission of product certificate: see sections 3.8 and 4.9 of the guidelines.

Validity of product certificate: see section 3.9 of the guidelines.

When to request a product certificate: see section 3.5 of the guidelines.

product information
The approved product information referred to in item 4.7 of the guidelines and item 2.A.5 of the Product Certificate. It normally consists of information for health professionals and the public (patient information leaflets), as approved in the exporting country, and when available, a data sheet or a Summary of Product Characteristics (SPC) approved by the regulatory authority.

product licence
An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product. It must set out, *inter alia*, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using

International Nonproprietary Names or national generic names where they exist), the shelf-life and storage conditions and packaging characteristics. It also contains all information approved for health professionals and the public (except promotional information), the sales category, the name and address of the licence holder, and the period of validity of the licence.

product licence holder
See licence holder.)

**production*
All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

registration
Any statutory system of approval required at national level as a precondition for introducing a pharmaceutical product onto the market.

registration certificate
See *product licence*.

specifications
See Appendix 3, explanatory note 7.

statement of licensing status
See item 3.13 of the guidelines and Appendix 2)

Summary Basis of Approval
The document prepared by some national regulatory authorities that summarizes the technical basis on which the product has been licensed (see section 4.7 of the guidelines and explanatory note 9 of the Product Certificate contained in Appendix 1).

Summary Product Characteristics (SPC)
Product information as approved by the regulatory authority. The SPC serves as the basis for production of information for health personnel as well as for consumer information on labels and leaflets of medicinal products and for control of advertising (see also *Product information).*

tenders and brokers
See item 4.6 of the guidelines.

WHO responsibility
See item 5.4 of the guidelines.

Reference

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992: 18-22 (WHO Technical Report Series, No. 823).

Annex 3: *Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability[1]

[1] Also published, with minor editorial changes, as Annex 9 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1996 (WHO Technical Report Series, No.863).

Introduction

Multisource drug products need to conform to the same standards of quality, efficacy and safety required of the originator's product. In addition, reasonable assurance must be provided that they are, as intended, clinically interchangeable with nominally equivalent market products.

With some classes of product, including - most evidently - parenteral formulations of highly water soluble compounds, interchangeability is adequately assured by implementation of Good Manufacturing Practices and evidence of conformity with relevant pharmacopoeial specifications. For other classes of product, including many biologicals such as vaccines, animal sera, products derived from human blood and plasma, and product manufactured by biotechnology, the concept of interchangeability raises complex considerations that are not addressed in this document, and these products are consequently excluded from consideration. However, for most nominally equivalent pharmaceutical products (including most solid oral dosage forms), a demonstration of therapeutic equivalence can and should be carried out, and such assessment should be included in the documentation for marketing authorization.

During the International Conference of Drug Regulatory Authorities (ICDRA) held in Ottawa, Canada in 1991 and again in The Hague, The Netherlands in 1994, regulatory officials supported the proposal that WHO should develop global standards and requirements for the regulatory assessment, marketing authorization and quality control of interchangeable multisource (generic) pharmaceutical products. Based on these suggestions, WHO convened three consultations during 1993 and 1994 in Geneva which have led to formulation of the present guideline. Participants at the consultations included representatives of drug regulatory authorities, academia, and the pharmaceutical industry including the generic industry.

The objective of this guideline is not only to provide technical guidance to national drug regulatory authorities and to drug manufacturers on how such assurance can be provided, but also to create an awareness that in some instances failure to assure interchangeability can prejudice the health and safety of patients. This danger has recently been highlighted in a joint statement of WHO's Tuberculosis Programme and the International Union

against Tuberculosis and Lung Disease. *Inter alia*, this states that "studies of fixed-dose combinations containing rifampicin have shown that in some of the preparations the rifampicin was poorly absorbed or not absorbed at all". The message is that fixed dosage combinations containing rifampicin must be "demonstrably bioavailable".

Highly developed national drug regulatory authorities now routinely require evidence of bioavailability for a very large majority of solid oral dosage forms including those contained within WHO's Model List of Essential Drugs. WHO will assist small regulatory authorities, for whom this guideline is primarily intended, in determining relevant policies and priorities - in relation to both locally manufactured and imported products - by compiling and maintaining a list of preparations that are known to have given rise to incidents indicative of clinical inequivalence. It will also work to promote a technical basis for assuring interchangeability of multisource products within an international as well as a national context by proposing the establishment of international reference materials as comparators for bioequivalence testing.

This guideline refers to the marketing of pharmaceutical products that are intended to be therapeutically equivalent and thus interchangeable but produced by different manufacturers. The WHO Guideline should be interpreted and applied without prejudice to obligations incurred through existing international agreement on trade-related aspects of intellectual property rights (Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, Article 39).

Glossary

Definitions given below apply specifically to the terms used in this guide. They *may* have different meanings in other contexts.

bioavailability
The rate and extent of availability of an active drug ingredient from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine.

bioequivalence
Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, can be expected to be essentially the same.

dosage form
The form of the completed pharmaceutical product, e.g., tablet, capsule, elixir, injection, suppository.

therapeutic equivalence
Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and after administration in the same molar dose their effects, with respect to both efficacy and safety, will be essentially the same as can be derived from appropriate studies (bioequivalence, pharmacodynamic, clinical or *in vitro* studies).

generic product
The term "generic product" has somewhat different meanings in different jurisdictions and in this document use of the term is avoided as much as possible, and the term "multisource pharmaceutical product" (see definition below) has been applied. Generic products may be marketed either under the nonproprietary approved name or under a new brand (proprietary) name. They may sometimes be marketed in dosage forms and/or strengths different from those of the innovator products. However, where the term "generic product" had to be used in this document it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of patent or other exclusivity rights.

innovator pharmaceutical product
Generally, the innovator pharmaceutical product is that which was first authorized for marketing, (normally as a patented drug) on the basis of documentation of efficacy, safety and quality (according to contemporary requirements). When drugs have been available for many years, it may not be possible to identify an innovator pharmaceutical product.

interchangeable pharmaceutical product
An interchangeable pharmaceutical product is one which is therapeutically equivalent to a reference product.

multisource pharmaceutical products
Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

pharmaceutical equivalence
Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form that meet the same or comparable standards and are intended to be administered by the same route. However, pharmaceutical equivalence does not necessarily imply therapeutic equivalence as differences in the excipients and/or the manufacturing process can lead to differences in product performance.

reference product
A reference product is a pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available the product which is the market leader may be used as a reference product, provided it has been authorized for marketing and its efficacy, safety and quality has been established and documented.

Part One. Regulatory assessment of interchangeable multisource pharmaceutical products

1. General considerations

The national health authorities (national drug regulatory authority) should ensure that all pharmaceutical products subject to their control conform to acceptable standards of quality, safety and efficacy; and that all premises and practices employed to manufacture, store and distribute these products comply with GMP standards to ensure the continued conformity of the products to these requirements until such time as they are delivered to the end user.

These objectives can be accomplished effectively only if a mandatory system of marketing authorization for pharmaceutical products and licensing of their manufacturers, importing agents and distributors are in place and adequate resources are available for implementation. Health authorities in countries with limited resources have less capacity to undertake these tasks. To assure the quality of imported pharmaceutical products and drug substances, they are dependent on authoritative, reliable, and independent information from the drug regulatory authority of the exporting country. This information, including information on the regulatory status of a pharmaceutical product, and the manufacturer's compliance with GMP (see *WHO Good Manufacturing Practices for Pharmaceutical Products*, WHO Technical Report Series No.823, 1992, Annex 1, pp. 14-79) in the exporting country, is most effectively obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce which provides a channel of communication between regulatory authorities in the importing and exporting countries (Resolutions WHA41.18 and WHA45.29).

The essential functions and responsibilities of a drug regulatory authority are further elaborated by WHO in the

Guiding Principles for Small National Drug Regulatory Authorities (WHO Technical Report Series, No. 790: 64-79, 1990 and No. 825: 62-74, 1992).

2. Multisource products and interchangeability

There are often economic pressures favouring the use of generic products. In some cases this can result in the purchase on contract of generic products by procurement agencies without prior licensing by the drug regulatory authority. However, all pharmaceutical products, including generic products, should be used in a country only after approval by the appropriate drug regulatory authority. Equally, pharmaceutical products intended exclusively for export should be subjected by the regulatory authority of the exporting country to the same controls and marketing authorization requirements with regard to quality, safety and efficacy as pharmaceutical products intended for the domestic market in the exporting country.

Nominally equivalent interchangeable (generic) pharmaceutical products should contain the same amount of the same therapeutically active ingredients in the same dosage form and should meet required pharmacopoeial standards. However, they are usually not identical and in some instances their clinical interchangeability may be in question. Although differences in colour, shape and flavour are obvious and sometimes disconcerting to the patient, they are often inconsequential to the performance of the pharmaceutical product. However differences in sensitizing potential due to the use of different excipients and differences in stability and bioavailability could have obvious clinical implications. Regulatory authorities consequently need to consider not only the quality, efficacy and safety of such pharmaceutical products, but also their interchangeability. This concept of interchangeability applies not only to the dosage form but also to the instructions for use and even to the packaging specifications, when these are critical to stability and shelf-life.

Regulatory authorities should require that documentation of a generic pharmaceutical product addresses three sets of criteria. These relate to:

- manufacturing (GMP) and quality control;
- product characteristics and labelling; and
- therapeutic equivalence (see Part Two).

Assessment of equivalence will normally require an *in vivo* study, or a justification that such a study should not be required in a particular case. *In vivo* study approaches include bioequivalence studies, pharmacodynamic studies, and comparative clinical trials (see sections 10-12). In selected cases *in vitro* dissolution studies may be sufficient to provide some indication of equivalence (see section 13). The regulatory authority should be in a position to help local manufacturers by advising them on drugs that pose potential bioavailability problems and therefore need *in vivo* studies.

Examples of national requirements for *in vivo* studies for drugs included in the WHO Model List of Essential Drugs are given in Appendix 1.

3. Technical data for regulatory assessment

For pharmaceutical products indicated for standard, well-established uses and that contain established ingredients, the following elements of information should be contained among others in documentation for marketing authorization and for a computerized data retrieval system:

- name of the product;
- active ingredient(s) (by international nonproprietary name(s)); their source; description of manufacturing methods and in-process controls;
- type of dosage form;
- route of administration;

Requirements to Establish Interchangeability

- main therapeutic category;
- complete quantitative formula with justification and method of manufacture of the dosage form in accordance with WHO GMP;
- quality control specifications for starting materials, intermediates and the final dosage form product with validated analytical method;
- results of batch testing with batch number, manufacturing date, including, where appropriate, the batch(es) used in bioequivalence studies;
- indications, dosage, method of use;
- contraindications, warnings, precautions, drug interactions;
- use in pregnancy and other special groups of patients;
- adverse effects;
- overdosage;
- equivalence data (comparative bioavailability, pharmacodynamic or clinical studies and comparative *in vitro* dissolution tests);
- stability data, proposed shelf-life, recommended storage conditions;
- container, packaging, labelling including proposed product information;
- proposed method of distribution:controlled drug; prescription item; pharmacy sale; general sale;
- manufacturer; licensing status (date of most recent inspection, date of licence and who issued the licence);
- importer/distributor;
- regulatory status in the exporting country and, where available, summary documents of regulatory assessment from the exporting country; regulatory status in other countries.

If the dosage form is a novel one intended to modify the drug delivery, such as a prolonged-release tablet, or if a different route of administration is proposed, supporting data, including clinical studies, will normally be required.

4. Product information and promotion

The product information intended for prescribers and end users should be available for all generic products authorized for marketing. The content of this information should be approved as a part of the marketing authorization. This information should be updated based on current information. The wording and illustrations used in subsequent promotion of the product should be fully consistent with this approved product information. All promotional activities should respect the WHO Ethical Criteria for Medicinal Drug Promotion (Resolution WHA41.17, May 1988).

5. Collaboration between drug regulatory authorities

Bilateral or multilateral collaboration between the drug regulatory authorities assists countries with limited resources. Sharing responsibilities in assessment and enhancing mutual cooperation provides a wider spectrum of expertise for evaluation. Harmonization of registration requirements between the drug regulatory authorities for registration of generics can accelerate the approval process. Furthermore, an agreed mechanism of quality assurance in relation to the assessment work of collaborating agencies is vital.

6. Exchange of evaluation reports

When a company applies for marketing authorization in more than one country, exchange of evaluation reports on the same product from the same manufacturer can accelerate the adoption of sound decisions, at national level. Such exchange should take place only subject to the agreement of the company concerned. Appropriate measures for safeguarding confidentiality of data must apply.

Part Two. Equivalence studies needed for marketing authorization

7. Documentation of equivalence for marketing authorization

Pharmaceutically equivalent multisource pharmaceutical products must be shown to be therapeutically equivalent to one another in order to be considered interchangeable. Several test methods are available to assess equivalence, including:

(a) Comparative bioavailability (bioequivalence) studies, in which the active drug substance or one or more metabolites is measured in an accessible biologic fluid such as plasma, blood or urine.
(b) Comparative pharmacodynamic studies in humans.
Comparative clinical trials.
(d) *In vitro* dissolution tests.

Applicability of each of these four modalities is discussed in subsequent sections of this guideline and special guidance is provided to conduct an assessment of bioequivalence studies. Other modalities have been used to assess bioequivalence, such as bioequivalence studies in animals, but are not discussed in this guideline because this approach is not accepted worldwide.

Acceptance of any test procedure in the documentation of equivalence between two pharmaceutical products by a drug regulatory authority depends on many factors, including characteristics of the active drug substance and the drug product and availability of resources for the conduct of a specific type of study. Where a drug produces meaningful concentrations in an accessible biologic fluid, such as plasma, bioequivalence studies are preferred. Where a drug does not produce measurable concentrations in an accessible biologic fluid, comparative clinical trials or pharmacodynamic studies may be necessary to document equivalence. *In vitro* testing, preferably based on a documented *in vitro/in vivo* correlation, may sometimes provide some indication of equivalence between two pharmaceutical products (see section 3).

Additional criteria that indicate when equivalence studies are necessary are discussed in the following two sections of the guideline (8 and 9).

8. When equivalence studies are not necessary

For certain formulations and circumstances, equivalence between two pharmaceutical products may be considered self-evident with no further requirement for documentation. Examples include:

(a) When multisource pharmaceutical products are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations;
(b) When multisource pharmaceutical products are solutions for oral use, contain the active substance in the same concentration, and do not contain an excipient that is known or suspected to affect gastro-intestinal transit or absorption of the active substance;
(c) When multisource pharmaceutical products are a gas;
(d) When the multisource pharmaceutical products are powders for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above;
(e) When multisource pharmaceutical products are otic or ophthalmic products prepared as aqueous solutions and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;
(f) When multisource pharmaceutical products are topical products prepared as aqueous solutions and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations;
(g) When multisource pharmaceutical products are inhalation products or nasal sprays, tested to be administered with or without essentially the same device, prepared as aqueous solutions, and contain the

same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations. Special *in vitro* testing should be required to document comparable device performance of the multisource inhalation product.

For elements (e), (f) and (g) above, it is incumbent upon the applicant to demonstrate that the excipients in the multisource product are essentially the same and in comparable concentrations as those in the reference product. In the event this information about the reference product cannot be provided by the applicant and the drug regulatory authority does not have access to these data, *in vivo* studies should be performed.

9. When equivalence studies are necessary and types of studies required

Except for the cases illustrated in section 8, this guideline recommends that documentation of equivalence be requested by registration authorities for a multisource pharmaceutical product in which the product is compared to the reference pharmaceutical product. Studies must be carried out using the formulation intended for marketing (see also Part Seven).

In vivo studies

For certain drugs and dosage forms, *in vivo* documentation of equivalence, through either a bioequivalence study, a comparative clinical pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. Examples are listed below.

(a) Oral immediate release pharmaceutical products with systemic action when one or more of the following criteria apply:

  (i) indicated for serious conditions requiring assured therapeutic response;
  (ii) narrow therapeutic window/safety margin; steep dose-response curve;
  (iii) pharmacokinetics complicated by variable or incomplete absorption or absorption window, nonlinear pharmacokinetics, presystemic elimination/high first-pass metabolism >70%;
  (iv) unfavourable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability, etc.;
  (v) documented evidence for bioavailability problems related to the drug or drugs of similar chemical structure or formulations;
  (vi) where a high ratio of excipients to active ingredients exists.

(b) Non-oral and non-parenteral pharmaceutical products designed to act by systemic absorption (such as transdermal patches, suppositories, etc.).
(c) Sustained or otherwise modified release pharmaceutical products designed to act by systemic absorption.
(d) Fixed combination products (see WHO Technical Report Series No. 825, 1992) with systemic action.
(e) Non-solution pharmaceutical products which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc. application) and are intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence. This does not, however, exclude the potential need for drug concentration measurements in order to assess unintended partial absorption.

In cases (a) to (d) plasma concentration measurements over time (bioequivalence) are normally sufficient proof for efficacy and safety. In case (e) the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence.

In vitro studies

In certain circumstances (see also 13), equivalence may be assessed by the use of *in vitro* dissolution testing. Examples where dissolution testing may be considered acceptable include:

(a) Drugs for which *in vivo* studies (see above) are not required;
(b) Different strengths of a multisource formulation, when the pharmaceutical products are manufactured by the same manufacturer at the same manufacturing site, where:

the qualitative composition between the strengths is essentially the same;
the ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipients is the same;
an appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety); and
in case of systemic availability pharmacokinetics have been shown to be linear over the therapeutic dose range.

Although this guideline comments primarily on registration requirements for multisource pharmaceutical products, it is to be noted that *in vitro* dissolution testing may also be suitable to confirm unchanged product quality and performance characteristics with minor formulation or manufacturing changes after approval (see Part Six).

Part Three. Tests for equivalence

The bioequivalence studies, pharmacodynamic studies and clinical trials should be carried out in accordance with the provisions and prerequisites for a clinical trial, as outlined in the WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products, Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP). The text in the box which follows has been taken from the WHO GCP Guidelines:

1. Provisions and prerequisites for a clinical trial

1.1. Justification for the trial

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks/benefits of a particular clinical trial be thoroughly considered and that the chosen solutions be scientifically sound and ethically justified.

1.2. Ethical principles

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki and should respect three basic ethical principles, namely justice, respect for persons, beneficence (maximize benefits and minimize harms and wrongs) and non-maleficence (do no harm) as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) or laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles.

1.3. Supporting data for the investigational product

Preclinical studies that provide sufficient documentation of potential safety and eventual clinical application of a pharmaceutical product are a necessary prerequisite for a clinical trial. Information about manufacturing procedures and data from tests performed on the actual product should establish that the product is of suitable quality. The pharmaceutical, preclinical and clinical data should be adapted to the appropriate phase of the trial, and the amount of supporting data should be appropriate to the size and duration of the proposed trial. In addition, a compilation of information on safety and efficacy collected in previous and ongoing clinical trials elsewhere with the investigational product is vital for the planning and conduct of subsequent trials.

1.4. Investigator and site(s) of investigation

Each investigator should have appropriate expertise, qualifications and competence to undertake a proposed study and be familiar with pharmacokinetic theories underlying bioavailability studies. Prior to the trial, the investigator(s) and the sponsor should establish an agreement on the protocol, the monitoring, the auditing and on standard operating procedures (SOP), and the allocation of trial-related responsibilities. The logistics and premises of the trial site should comply with requirements for the safe and efficient conduct of the trial.

1.5. **Regulatory requirements**

Countries in which clinical trials are performed should have regulations by which these studies can be conducted. The pre-trial agreement between sponsor and investigator(s) should designate the parties responsible for meeting each applicable regulatory requirement (e.g. application, protocol amendments, adverse reaction reporting, notifications to ethics committee). All parties involved in a clinical trial should comply fully with the existing national regulations or requirements. In those countries where regulations do not yet exist or require supplementation, the relevant government officials may designate, in part or in whole, the WHO Guidelines for Good Clinical Practice as the basis on which clinical trials will be conducted.

2. **The protocol**

The clinical trial should be carried out in accordance with a protocol agreed upon and signed by the investigator and the sponsor. Any change(s) subsequently required must be similarly agreed on and signed by the investigator and sponsor and appended as amendments. The protocol and attachments/appendices should state the aim of the trial and the procedures to be used; the reasons for proposing that it should be undertaken on human subjects; the nature and degree of any known risks; the groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent.

The protocol and attachments/appendices should be scientifically and ethically appraised by one or - if required by local laws and regulations - more, review bodies (institutional review board, peer review committee, ethics committee, drug regulatory authority, etc.), constituted appropriately for these purposes and independent of the investigator(s) and sponsor.

(For additional information see WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products.)

10. **Bioequivalence studies in humans**

Bioequivalence studies are designed to compare the *in vivo* performance of a test pharmaceutical product (multisource) compared to a reference pharmaceutical product. A common design for a bioequivalence study involves administration of the test and reference products on two occasions to volunteer subjects, with each administration separated by a wash-out period. The wash-out period is chosen to ensure that drug given in one treatment is entirely eliminated prior to administration of the next treatment. Just prior to administration and for a suitable period afterwards, blood and/or urine samples are collected and assayed for concentration of the drug substance and/or one or more metabolites. The rise and fall of these concentrations over time in each subject in the study provide an estimate of how the drug substance is released from the test and reference products and absorbed into the body. To allow comparisons between the two products, these blood (to include plasma or serum) and/or urine concentration time curves are used to calculate certain bioequivalence metrics of interest. Commonly used metrics are the area under the blood (plasma or serum) concentration time curve (AUC) and peak concentration. These metrics are calculated for each subject in the study and the resulting values are compared statistically. Details of the general approach are provided in the following sections.

Subjects

Selection of subjects

Requirements to Establish Interchangeability
The subject population for bioequivalence studies should be as homogenous as possible and therefore studies should generally be performed with healthy volunteers in order to reduce variability other than in the pharmaceutical products. Clear criteria for inclusion/exclusion should be stated. If feasible, they should belong to both genders (however, the risk to women will need to be considered on an individual basis and, if necessary, a warning issued to them about any possible dangers to the foetus if they should become pregnant). They should normally be in the age range of 18-55 years with a weight within the normal range according to accepted life tables. The subjects should preferably be non-smokers and without a history of alcohol or drug abuse problems. If smokers are included they should be identified as such. The suitability of the volunteers should be screened using standard laboratory tests, a medical history, and a physical examination. If necessary, special medical investigations may be carried out before and during studies depending on the pharmacology of the individual drug being investigated.

In case the aim of the bioequivalence study is to address specific questions (e.g., bioequivalence in a special population) the selection criteria have to be adjusted accordingly.

Genetic phenotyping
Phenotyping and/or genotyping of subjects may be considered for safety reasons.

Patients versus healthy volunteers
If unacceptable pharmacological effects or risk may ensue because of known adverse effects of the active substance for healthy volunteers, it may be necessary to use patients under treatment rather than healthy volunteers. This alternative should be explained by the sponsor.

Monitoring the health of subjects during the study
During the study, the health of volunteers should be monitored so that onset of side effects, toxicity, or any intercurrent disease may be recorded, and appropriate measures taken.

Health monitoring before, during and after the study must be carried out under the supervision of a qualified medical practitioner licensed in the jurisdiction in which the study takes place.

Design

General study design
The study should be designed so as to set test conditions which reduce intra- and inter-subject variability and avoid biased results. Standardization (exercise, diet, fluid intake, posture, restriction of the intake of alcohol, caffeine, certain fruit juices, and concomitant drugs in the time period before and during the study) is important to minimize the magnitude of variability other than in the pharmaceutical products.

A cross-over design with randomized allocation of volunteers to each leg is the first choice for bioequivalence studies. The design of studies should, however, depend on the type of drug, and other designs may be more appropriate for specific cases, for example, highly variable drugs and those with a long half-life. In cross-over studies a wash-out period between administration of the test product and the reference product of more than five times the dominant and/or terminal drug half-life is usual, but special consideration will need to be given to extending this period if active metabolites with longer half-lives are produced and under other circumstances.
The administration of the product should be standardized with a defined time of day for ingestion, volume of fluid (150 ml is usual) and usually in the fasting state.

Parameters to be assessed
In bioavailability studies the shape of, and the area under, the plasma concentration curve, or the profile of cumulative renal excretion and excretion rate are mostly used to assess extent and rate of absorption. Sampling points or periods should be chosen such that the time *versus* concentration profile is adequately defined to allow calculation of relevant parameters. From the primary results the bioavailability parameters desired are derived,

such as AUC_{∞}, AUC_t, C_{max}, t_{max}, Ae_{∞}, Ae_t, dAe/dt, or any other justifiable parameters (see Appendix 2). The method of calculating AUC-values should be specified. AUC_{∞} and C_{max} are considered to be the most relevant parameters for assessment of bioequivalence. In case of use of urine excretion data this corresponds to Ae_{∞} and dAe/dt_{max}. For additional information $t_{½}$ and MRT can be calculated. For steady-state studies AUC_{τ}, and % peak trough fluctuation can be calculated. The exclusive use of modelled parameters is not recommended unless the pharmacokinetic model has been validated for the active substance and the products.

Additional considerations for complicated drugs
Drugs which would show unacceptable pharmacological effects in volunteers (e.g., serious adverse events, or where the drug is toxic or particularly potent or the trial necessitates a high dose) may require crossover studies in patients or sometimes parallel group design studies in patients.

Drugs with long half-lives may require a parallel design or the use of truncated Area Under Curve (AUC_t) data or a multi-dose study. The truncated area should cover the absorption phase.

Drugs for which the rate of input into the systemic circulation is important may require the collection of more samples around the time of the t_{max}.

Multi-dose studies may be helpful to assess bioequivalence for:

- drugs with non-linear kinetics (including those with saturable plasma protein binding);
- cases where the assay sensitivity is too low to cover a large enough portion of the AUC_{∞};
- drug substance combinations, if the ratio of plasma concentrations of the individual drug substances is important;
- controlled-release dosage forms;
- highly variable drugs.

Number of subjects
The number of subjects required for a sound bioequivalence study is determined by the error variance associated with the primary parameters to be studied (as estimated from a pilot experiment, from previous studies or from published data), by the significance level desired, and by the deviation from the reference product compatible with bioequivalence and with safety and efficacy. It should be calculated by appropriate methods (see page 124) and should not normally be smaller than 12. In most of the cases 18-24 subjects may be needed (see Diletti E, Hauschke D, Steinijans VW,: Sample size determination for bioequivalence assessment by means of confidence intervals. Int J Clin Pharmacol Ther and Toxicol, 1991, 29:1-8; Hauschke D, Steinijans VW, Diletti E, Burke M: Sample size determination for bioequivalence assessment using a multiplicative model. J Pharmacokin Biopharm, 1992, 20:559-563; and Phillips KE:

Power of the two one-sided tests procedure in bioequivalence. J Pharmacokin Biopharm, 1990, 18:137-144). The number of recruited subjects should always be justified.

Investigational products
Test products (samples) used in the bioequivalence studies for registration purposes should be identical to the projected commercial pharmaceutical product. Therefore not only the composition and quality characteristics (including stability) but also manufacturing methods should copy those in the future routine production runs.

Samples ideally should be taken from batches of industrial scale. When this is not feasible, pilot or small-scale production batches may be used provided that they are not smaller than one tenth (10%) of expected full production batches.

It is recommended that potency and *in vitro* dissolution characteristics of the test and reference pharmaceutical products be ascertained prior to performance of an equivalence study. Contents of the active drug substance(s)

between the two products should not differ by more than +/-5%. If the potency of the reference material deviates from the declared content of 100% by more than 5%, this difference may be used subsequently to dose-normalize certain bioavailability metrics in order to facilitate comparisons between the test and reference pharmaceutical products.

Studies of metabolites

Use of metabolite data in bioequivalence studies requires careful consideration. Generally, evaluation of bioequivalence will be based upon the measured concentrations of the pharmacologically active drug substance and its active metabolite(s) if present. If it is impossible to measure the active drug substance, a major biotransformation product may be used. The measurement of concentrations of biotransformation product is essential if the substance studied is a prodrug. If urinary excretion (rate) is measured, the product determined should represent a major fraction of the dose. Although measurement of a major active metabolite is usually acceptable, measurement of inactive metabolite can only rarely be justified.

Measurement of individual isomers for chiral drug substance products

A non-stereoselective assay is currently acceptable for bioequivalence studies. Under certain circumstances, assays that distinguish between the enantiomers of a chiral drug substance may be appropriate.

Validation of analytical test methods

All analytical test methods must be well-characterized, fully validated and documented. They should meet requirements of specificity, accuracy, sensitivity and precision. Knowledge of the stability of the active substance and/or its biotransformation product in the sample material is a prerequisite for obtaining reliable results. For this item reference is made to Conference Report on Analytical Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies, Pharmaceutical Research, Vol.9, No.4, 1992. Results of validation should be reported. Some important points are:

- validation comprises before-study and within-study phases;
- validation must cover the intended use of the assay;
- the calibration range must be appropriate to the study samples;

- if an assay is to be used at different sites, it must be validated at each site and cross-site comparability established;
- an assay which is not in regular use requires sufficient revalidation to show that it is performed according to the original validated test procedures. The revalidation study must be documented, usually as an appendix to the study report;
- within a study, the use of two or more methods to assay samples in the same matrix over a similar calibration range is strongly discouraged;
- if different studies are to be compared and the samples from the different studies have been assayed by different methods and the methods cover a similar concentration range and the same matrix, then the methods should be cross-validated.

Results of validation should be reported.

Reserve samples

Sufficient samples of each batch of the pharmaceutical products used in the studies, and a record of their analyses and characteristics, must be kept for reference under appropriate storage conditions as guided by national regulations. When specifically requested these reserve samples may be required by the authorities to recheck the products.

Statistical analysis and acceptance criteria

General consideration

The primary concern in bioequivalence assessment is to limit the risk of a false declaration of equivalence. Thus the risk (α) is that which the regulatory agencies are willing to accept for erroneously concluding equivalence.

The statistical methods of choice at present are the two one-sided tests procedure (see Schuirmann, DJ, J. Pharmacokinet Biopharm, 1987;15:657-680) or to derive a parametric or non-parametric 100 (1-2α)% confidence interval for the quotient $\mu T/\mu R$ of the test and the reference pharmaceutical product. Alpha is set at 5% leading, in the parametric case, to the shortest (conventional) 90% confidence interval based on an analysis of variance or, in the non-parametric case, to the 90% confidence intervals (see also Hauschke D et al: International J Clin Pharmacol Ther Toxicol, 1990; 28:72-78 and Hollander M, Wolfe DA, Nonparametric Statistical Methods, New York: John Wiley & Sons 1973, Chapter 4.3.).

The statistical procedures should be specified before the data collection starts (see Appendix 3). The procedures should lead to a decision scheme which is symmetrical with respect to the two formulations (i.e., leading to the same decision whether the new formulation is compared to reference product or reference product to the new formulation).

Concentration and concentration-related quantities e.g., AUC and C_{max}, should be analysed after logarithmic transformation. t_{max} will usually be analysed without such transformation.

For t_{max} normally descriptive statistics should be given. If t_{max} is to be subjected to a statistical analysis this should be based on non-parametric methods. Other parameters may also be evaluated by non-parametric methods, in which case descriptive statistics should be given that do not require specific distributional assumptions, e.g., medians instead of means.

Assumptions of the design or analysis should be addressed, and the possibility of differing variations in the formulations should be investigated. This covers investigation of period effects, sequence or carry-over effects, and homogeneity of variance (homoscedascity).

Outlying observations should be reviewed for their impact on the conclusions. Medical or pharmacokinetic explanations for such observations should be sought.

Acceptance ranges

Regarding AUC, the 90% confidence interval should generally be within the acceptance range 80 to 125%. For drugs with a particularly narrow therapeutic range, the AUC acceptance range may need to be smaller, and this should be justified clinically.

C_{max} does not characterize the rate of absorption particularly well in many cases and there is no consensus on any other concentration-based parameter which might be more suitable. The acceptance range for C_{max} may be wider than for the AUC (see Appendix 3).

Reporting of results

The report of a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with Good Clinical Practice rules (see WHO Guideline for GCP for Trials on Pharmaceutical Products). The responsible investigator(s) should sign for their respective sections of the report. Names and affiliations of the responsible investigator(s), site of the study and period of its execution should be stated. The names and batch numbers of the pharmaceutical products used in the study as well as the

composition(s) of the tests product(s) should be given. The analytical validation report should be attached. Results of *in vitro* dissolution tests should be provided. In addition, the applicant should submit a signed statement confirming the identity of the test product with the pharmaceutical product which is submitted for registration.

All results should be presented clearly. The procedure for calculating the parameters used (e.g., AUC) from the raw data should be stated. Deletion of data should be justified. If results are calculated using pharmacokinetic models, the model and the computing procedure used should be justified. Individual plasma concentration/time curves should be drawn on a linear/linear, and facultatively also on a lin/log scale. All individual data and results should be given, also of eventually dropped-out subjects. Drop-out and withdrawal of subjects should be reported and accounted for. Test results of representative samples should be included.

The statistical report should be sufficiently detailed, so as to enable the statistical analyses to be repeated if necessary. If the statistical methods applied deviate from those specified in the trial protocol, the reasons for the deviations should be stated.

11. **Pharmacodynamic studies**

Studies in healthy volunteers or patients using pharmacodynamic measurements may be used for establishing equivalence between two pharmaceutical products. These studies may become necessary if quantitative analysis of the drug and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurements of drug concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product e.g., for topical products without an intended absorption of the drug into the systemic circulation.
If pharmacodynamic studies are to be used they must be performed as rigorously as bioequivalence studies, and the principles of GCP (see WHO Guideline for GCP for Trials on Pharmaceutical Products) must be followed.

The following requirements must be recognized when planning, conducting and assessing the results of a study intended to demonstrate equivalence by means of measuring pharmacodynamic drug responses.

- The response which is measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety.
- The methodology must be validated for precision, accuracy, reproducibility and specificity.
- Neither the test nor the reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses which give maximum or near-maximum effects. Investigation of dose-response relationships may be a necessary part of the design.
- The response should be measured quantitatively under double blind conditions and be recordable in an instrument-produced or instrument-recorded fashion on a repetitive basis to provide a record of the pharmacodynamic events which are substitutes for plasma concentrations. In those instances where such measurements are not possible, recordings on visual analogue scales may be used. In other instances where the data are limited to qualitative (categorized) measurements appropriate special statistical analysis will be required.
- Non-responders should be excluded from the study by prior screening. The criteria by which responders *versus* non-responders are identified must be stated in the protocol.
- In instances where an important placebo effect can occur, comparison between pharmaceutical products can only be made by *a priori* consideration of the placebo effect in the study design. This may be achieved by adding a third phase with placebo treatment in the design of the study.
- The underlying pathology and natural history of the condition must be considered in the study design. There should be knowledge of the reproducibility of base-line conditions.
- A cross-over design can be used. Where this is not appropriate a parallel group study design should be

chosen.

In studies in which continuous variables could be recorded, the time course of the intensity of the drug action can be described in the same way as in a study in which plasma concentrations were measured, and parameters can be derived which describe the area under the effect-time curve, the maximum response and the time when maximum response occurred.

The statistical considerations for the assessment of the outcome of the study are in principle, the same as outlined for the bioequivalence studies. However, a correction for the potential non-linearity of the relationship between the dose and the area under the effect-time curve should be performed on the basis of the outcome of the dose-ranging study as mentioned above. However, it should be noted that the conventional acceptance range as applied for bioequivalence assessment is not appropriate (too large) in most of the cases but should be defined on a case-by-case basis and described in the protocol.

12. *Clinical trials*

In several instances (see example (e) p. 117) plasma concentration time-profile data are not suitable to assess equivalence between two formulations. Whereas in some of the cases pharmacodynamic studies can be an appropriate tool for establishing equivalence (see section 11), in other instances this type of study cannot be performed because of lack of meaningful pharmacodynamic parameters which can be measured and a comparative clinical trial has to be performed in order to demonstrate equivalence between two formulations.

However, if a clinical study is considered as being undertaken to prove equivalence the same statistical principles apply as for the bioequivalence studies. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects in bioequivalence studies.

The following items are important and need to be defined in the protocol in advance:

The methodology issues for establishing equivalence between pharmaceutical products by means of a clinical trial in patients with a therapeutic endpoint have not yet been discussed as extensively as for bioequivalence trials. However, important items can be identified which need to be defined in the protocol:

(a) The target parameters which usually represent relevant clinical end-points from which the intensity and the onset, if applicable and relevant, of the response are to be derived.
(b) The size of the acceptance range has to be defined case by case taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance range in clinical trials cannot be based on a general consensus on all the therapeutic classes and indications.
(c) The presently used statistical method is the confidence interval approach. The main concern is to rule out that the test product is inferior to the reference pharmaceutical product by more than the specified amount. Hence, a one-sided confidence interval (for efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.
(d) Where appropriate, a placebo leg should be included in the design.
(e) In some cases, it is relevant to include safety end-points in the final comparative assessments.

13. *In Vitro* dissolution

Comparative *in vitro* dissolution studies may be useful in the documentation of equivalence between two multisource pharmaceutical products. Because of many limitations associated with the use of *in vitro* dissolution in the documentation of equivalence this guidelines recommends that its application for this purpose be kept to a minimum. Hence, *in vitro* dissolution testing as the sole documentation of equivalence is not applicable to drugs that fall within the criteria of the pharmaceutical products listed on p. 117 from (a) to (e). This approach should also be reserved for rapidly dissolving drug products.[1] When such multisource test and reference products, both dissolve with sufficient rapidity (e.g., >80% in 15 minutes), their *in vivo* equivalence may be presumed. Approval of multisource formulations using comparative *in vitro* dissolution studies should be based on generation of comparative dissolution profiles rather than single point dissolution tests, such as are

[1] Where a drug substance and drug product do not dissolve with sufficient rapidity, as noted above, *in vitr* dissolution methods might still be used to document equivalence using appropriately validated dissolutio methodology to include a *in vitro/in vivo* correlation. Such methodology should derive from development an application of specifications and statistical methods to define nonequivalence. This development may requi formulations with different *in vivo* performance characteristics. With such formulations, discriminating *in vitr* dissolution tests for use in equivalence studies may be developed. With these additional requirements, howeve performance of a standard *in vivo* bioequivalence as described in V.1 may be preferable.

described in various compendia. Multiple dissolution test conditions and physiologically relevant media are recommended.

Part Four. *In vitro* dissolution tests in product development and quality control

In vitro dissolution tests are valuable in product development and to monitor batch to batch consistency of the manufacturing process following approval to market. *In vitro* dissolution test results are also used to test release characteristics of a dosage form in storage, i.e., to measure stability of the release rate. Dissolution testing may be considered as a useful check for several characteristics of the dosage form, to include:

- particle size distribution, state of hydration, crystal form and other solid state properties of the active ingredients;
- mechanical properties of the form itself (water content, resistance to crushing force for tablets, integrity of the shell for capsules and coated tablets, etc.).

When used in product quality control, information about *in vitro* dissolution should be provided in the documentation for marketing authorization. *In vitro* dissolution tests and specifications for quality control should be based either on suitable compendial specifications or on the *in vitro* performance of the test batches used to generate material for the equivalence study. Where sufficient full-scale process validation batches are not prepared in the immediate post-approval period, several batches (two or three are recommended) of the test product should be manufactured in the pre-approval period according to standard, consistent, well-documented procedures. Two of these batches should contain at least 100,000 units or 10% of the intended production batch, whichever is larger. The third, if prepared, may be smaller (e.g., 25,000 units). Justification should be provided if smaller batches are used. Material from these test batches is used both to provide material for dissolution studies and also for equivalence testing. Dissolution tests on these batches should be based on physiologically relevant media and test conditions. When deciding upon the test methods to be used, it is recommended to start experiments with widely-used compendial methods "paddle" and "basket", and try other methods ("flow through cell" etc.) when these fail to demonstrate sufficient discriminatory power. Dissolution profiles are recommended, even when a single point compendial dissolution test is available. In case of immediate release pharmaceutical products a single point dissolution may be used for quality control purposes. Specifications of the dissolution performance of subsequently manufactured batches will be based on the results of the dissolution tests performed on the test batches. Whereas it is undisputed that the value of dissolution testing will be enhanced if the dissolution results can be shown to reflect important changes in formulation and/or the manufacturing process by *in vivo* studies the practicalities are still under discussion. It is not recommended to broaden the dissolution specification based on the performance of the test batches beyond the point where equivalence between the test material used in the equivalence study and subsequently manufactured production batches can no longer be assumed.

The following data should be recorded and included in the documentation for marketing authorization:

(a) Comparative dissolution results for test and reference pharmaceutical products after intervals appropriate for products and conditions under investigation (normally a minimum three sampling times).
(b) For each sampling time, the observed data, individual values, the range and the coefficient of variation (relative standard deviation) should be reported.

Part Five. Clinically important variations in bioavailability leading to non-approval of the product

A new formulation with a bioavailability outside the acceptance range compared to an existing pharmaceutical product is not interchangeable by definition. A marketing authorization for a formulation with a lower bioavailability may be non-approved on the basis of efficacy concerns.
A marketing authorization for a formulation with a higher bioavailability ("suprabioavailability") may be non-approved on the basis of safety concerns. In the latter case there are two options:

Requirements to Establish Interchangeability

A new formulation with increased bioavailability compared to an existing pharmaceutical product is defined as being "suprabioavailable". Options in this situation are:

(i) The dosage form, if reformulated to be bioequivalent with the existing pharmaceutical product could be accepted as interchangeable with the existing pharmaceutical product. This may not be ideal as dosage forms with low bioavailability tend to be variable in performance.

(ii) A dosage form with the content of active substance reduced to allow for the increased bioavailability could be accepted as a new (improved) dosage form. This would normally need to be supported by clinical trial data. Such a pharmaceutical product must not be accepted as interchangeable with the existing pharmaceutical product, and would normally become the reference product for future interchangeable pharmaceutical products. The name of the new pharmaceutical product should preclude confusion with the older approved pharmaceutical product(s).

Part Six. Studies needed to support new post-marketing manufacturing conditions

With all pharmaceutical products, in case of post-marketing changes extensive *in vitro* and/or *in vivo* testing may be required. Such changes include changes in: (i) formulation; (ii) site of manufacture; (iii) process of manufacture; and (iv) manufacturing equipment. The types and extent of further testing required depend on the magnitude of the changes made. If a major change is made, the product might become a new pharmaceutical product, if the national authorities so decide.

Part Seven. Choice of reference product

The innovator pharmaceutical product is usually the most logical reference product for related generics because, in general, its quality will have been well assessed and its efficacy and safety will have been securely established in clinical trials and post-marketing monitoring schemes. There is, however, currently no global agreement on the selection of a reference product. The selection is made variably at national level by the drug regulatory authority having regard either to the most widely used "leading" product within the market or the pharmaceutical product that was first to be approved within that market. The possibility exists for significant differences to emerge between reference products adopted in different countries.

This being so, consideration needs to be given to the feasibility of developing reference materials on a global basis. Representative bodies of the pharmaceutical industry and other interested parties should be invited to collaborate in the preparation, maintenance and international acceptance of a system of international reference standards for pharmaceutical products with defined quality and bioavailability characteristics.

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Appendix 1
Examples of national requirements for *in vivo* equivalence of studies for drugs included in the WHO Model List of Essential Drugs (Canada, Germany and the USA, December 1994)

General

National requirements for equivalence studies for specific drug products differ from country to country. National decisions for the requirement of equivalence studies of a specific drug product can be based on any of the following:

- case by case study;
- criteria established by a national advisory committee; or
- application of the national regulatory guidelines.

A list of examples is presented in Table l. It is intended to be illustrative only, in accordance with the guidelines, and does not represent a formal recommendation.

The list is based on substances and products included in the WHO Model List of Essential Drugs (*1*), but only includes essential drugs for which *in vivo* studies are required because of the nature of the dosage form. Some dosage forms, e.g. solutions and injections, have therefore been omitted from the list as they have not been identified as requiring studies in one of the three countries covered.

Examples of decisions on criteria taken by national authorities:

Canada
At present, demonstration of bioequivalence is required for those drugs which are not considered to have been marketed in Canada for their intended purpose(s) for sufficient time, and in sufficient quantity to establish safety and efficacy (new drugs). Bioequivalence may be demonstrated by comparative bioequivalence studies or by clinical studies including, where applicable, acceptable surrogate models. Scientific criteria, similar to those of the European community and Australia, are being developed for deciding in which situations *in vivo* demonstration of bioequivalence is required for drugs that are not new.

Germany
Over the past years, the National Advisory Committee has taken the decision on the need for a comparative bioavailability/bioequivalence study as a requirement for marketing authorization. These decisions have been based on published data for the drug substance and its dosage form, and on the use of an algorithm. Details of the algorithm, the criteria and the resulting decisions have been published in the German Federal Register. In certain circumstances, the regulatory authority takes decisions on a case-by-case basis.

USA
Drug products introduced before 1938 in USA do not require an approval for marketing and therefore no *in vivo* equivalence study is needed. The majority of drug products other than solution dosage forms, approved between 1938 and 1962, and known to have potential bioavailability problems, require *in vivo* equivalence studies. Generally, drug products approved after 1962, with the exception of solution dosage forms require *in vivo* equivalence studies.

Table 1

Examples of national requirements for equivalence studies [1]

Drug substance	Dosage form	Canada	Germany	USA

acetazolamide	tablet, 250 mg	+b	+b	+b
acetylsalicylic acid	suppository, 50-150 mg	?	+b	-
	tablet, 100-500 mg -	+b	-	
albendazole	tablet, 200 mg	o	+b	o
allopurinol	tablet, 100 mg	+b	+b	+b
aluminium hydroxide	oral suspension, 320 mg/5 ml	-	+p	-
	tablet, 500 mg	-	+p	-
amiloride hydrochloride	tablet, 5mg	+b	-	+b
aminobenzoic acid	cream	?	+p+c	-
	gel	?	+p+c	-
	lotion	?	+p+c	-
aminophylline	tablet, 100 mg, 200 mg	?	o	+b
amitriptyline hydrochloride	tablet, 25 mg	?	+b	+b
amoxicillin	capsule, 250 mg, 500 mg	+b	+b	+b
	powder for oral suspension, 125 mg/5 ml	+b	+b	+b
	tablet, 250 mg, 500 mg	+b	+b	+b
ascorbic acid	tablet, 50 mg	-	?	-
atenolol	tablet, 50 mg,100 mg	+b	-	+b
atropine sulfate	solution (eye drops), 0.1%, 0.5%, 1%	o	+c	-
	tablet, 1 mg	o	?	o
azathioprine	tablet, 50 mg	+b	+b	+b

[1] +*: in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials;
-: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp. 118-128.

Table 1 (continued,
Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
bacitracin zinc	ointment, 500 IU + neomycin sulfate, 5 mg/g	o	+c	-
beclometasone dipropionate	inhalation, 50 µg/dose	?	+p+c	+p
benzathine benzylpenicillin	powder for injection,1.44 g of benzylpenicillin (= 2.4 million IU) in 5-ml vials	o	-	+b
benznidazole	tablet, 100 mg	o	+b	o
benzoic acid	cream, 6% + salicylic acid, 3%	-	+p+c	o
	ointment, 6% + salicylic acid, 3%	-	+p+c	-
benzoyl peroxide	cream, 5%	-	+p+c	-
lotion, 5%	-	+p+c		
benzyl benzoate	lotion, 25% -	+p+c	o	
betamethasone	cream, 0.1% of betamethasone	+p	+p+c	+p
valerate	ointment, 0.1% of betamethasone	+p	+p+c	+p
biperiden hydrochloride	tablet, 2 mg	+b	+b	+b
calamine	lotion	-	+p+c	-
calcium folinate	tablet, 15 mg	+b	o	+b
captopril	tablet, 25 mg	+b	-	+b
carbamazepine	tablet, 100 mg, 200 mg	+b	+b	+b
carbidopa	tablet, 10 mg + levodopa,100 mg	+b	+b	+b
	25 mg + levodopa, 250 mg	+b	+b	+b
chloramphenicol	capsule, 250 mg	?	+b	+b
chloramphenicol palmitate	oral suspension, 150 mg of chloramphenicol/5 ml	?	+b	+b
chloramphenicol sodium succinate	oily suspension, injection 0.5 g of chloramphenicol/ml in 2-ml ampoule	o	+b	o
chloroquine hydrochloride	injection, 40 mg of chloroquine/ml in 5-ml ampoule	o	-	-
chloroquine phosphate	tablet, 150 mg of chloroquine	o	+b	-
chloroquine sulfate	tablet, 150 mg of chloroquine	o	+b	o

' +: *in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials;
-: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp.118-128.

Table 1 (continued),

Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
chlorphenamine hydrogen maleate	tablet, 4 mg	-	?	-
chlorpromazine hydrochloride	tablet, 100 mg	?	+b	+b
ciclosporin	capsule, 25 mg	+b	+b	+b
cimetidine	tablet, 200 mg	+b	-	+b
ciprofloxacin hydrochloride	tablet, 250 mg of ciprofloxacin	+b	+b	+b
clofazimine	capsule, 50 mg, 100 mg	o	+b	+b
clomifene citrate	tablet, 50mg	+b	+b	+b
clomipramine hydrochloride	capsule, 10 mg, 25 mg	+b	o	+b
cloxacillin sodium	capsule, 500 mg of cloxaxillin	?	+b	+b
codeine phosphate	tablets, 10 mg, 30 mg	o	-	-
colchicine	tablet, 500 µg	?	+b	-
cyclophosphamide	tablet, 25 mg	+b	+b	+b
dapsone	tablet, 50 mg,100 mg	?	+b	+b
desmopressin acetate	nasal spray, 10 µg/metered dose	+b+p	+p+c	?
dexamethasone	tablet, 500 µg, 4 mg	?	?	+b
diazepam	scored tablet, 2 mg, 5 mg	+b	-	+b
diethylcarbamazine dihydrogen citrate	tablet, 50 mg	o	+b	+b
digitoxin	tablet, 50 µg,100 µg	?	+b	-
digoxin	tablet, 62.5 µg, 250 µg	?	+b	-
diloxanide furoate	tablet, 500 mg	o	+b	o
dimercaprol	injection, in oil, 50 mg/ml in 2-ml ampoule	+b+c	+b[2]	-
dioxybenzone	cream	?	+p+c	o
	lotion	?	+p+c	o
	gel	?	+p+c	o
dithranol	ointment, 0.1-2%	-	+p+c	-

[1]+: *in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials;
-: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending, o: no information available, no final decision taken, or not available on national market. See also pp.118-128.

[2] "Depot" preparation for injection.

Table 1 (continued)

Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
doxycycline hyclate	capsule, 100 mg of doxycycline	+b	+b	+b
	tablet, 100 mg of doxycycline	+b	+b	+b
ergocalciferol	capsule, 1.25 mg (50 000 IU)	o	+b	-
	tablet, 1.25 mg (50000 IU)	o	+b	-
ergometrine hydrogen maleate	tablet, 200 µg	?	+b	-
ergotamine tartrate	tablet, 2 mg	o	+b	-
erythromycin ethylsuccinate	capsule, 250 mg of erythromycin	?	+b	+b
	powder for oral suspension, 125 mg of erythromycin	?	+b	+b
	tablet, 250 mg of erythromycin	?	+b	+b
erythromycin stearate	capsule, 250 mg of erythromycin	?	+b	+b
	powder for oral suspension, 125 mg of erythromycin	?	+b	+b
	tablet, 250 mg of erythromycin	?	+b	+b
ethambutol hydrochloride	tablet, 100-400 mg +b	+b	+b	
ethinylestradiol	tablet, 50 µg	+b	+b	+b
	tablet, 30µg + levonorgestrel 150 µg	+b	+b	+b
	50 µg + levonorgestrel, 250 µg	+b	+b	+b
	tablet, 35 µg + norethisterone, 1.0 mg	+b	+b	+b
ethosuximide	capsule, 250 mg	?	+b	+b
etoposide	capsule, 100 mg	+b	+b	+b
ferrous sulfate	tablet, 60 mg of Fe - folic acid, 250 µg	o	-	
	tablet, 60 mg of Fe+	-	o	-
flucytosine	capsule, 250 mg	+b	+b	+b
fludrocortisone acetate	tablet, 100 µg	+b	+b	+b
fluorouracil	ointment, 5%	+c	+p+c	?
fluphenazine decanoate	injection, 25 mg in 1-ml ampoule	?	+b[2]	-
fluphenazine enantate	injection, 25 mg in 1-ml ampoule	?	+b[2]	-

[1] *+: in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials;
-: no *in vivo* studies required; ?: decision on the type of *in* vivo studies pending; o: no information available, no final decision taken, or not available on national market. See also pp.118-128.

[2] "Depot" preparation for injection.

Table 1 (continued)

Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
folic acid	tablet, 5 mg,1 mg	+b	+b	-
	tablet, 250 µg + ferrous sulfate, 60 mg of Fe	-	+b	-
furosemide	tablet, 40mg	+b	+b	+b
gentamicin sulfate	solution (eye drops), 0.3%	+c	+p+c	-
glyceryl trinitrate	tablet (sublingual), 500 µg	?	+b	-
griseofulvin	capsule, 125 mg, 250 mg	?	+b	+b
	tablet,125 mg, 250 mg	?	+b	+b
haloperidol	tablet, 2 mg, 5 mg	+b	-	+b
hydralazine hydrochloride	tablet, 25 mg, 50 mg	o	+b	-
hydrochlorothiazide	tablet, 25 mg, 50 mg	?	-	+b
hydrocortisone acetate	cream,1%	o	+p+c	-
	ointment, 1%	o	+p+c	-
	suppository, 25 mg	o +p+c	?	
ibuprofen	tablet, 200 mg	+b	-	+b
idoxuridine	eye ointment, 0.2%	o	+p+c	+c
	solution (eye drops) 0.1 %	o	-	-
indometacin	capsule, 25 mg	+b	-	+b
	tablet, 25 mg	+b	-	o
insulin:				
insulin (soluble)	injection, 40 lU/ml in 10-ml vial,	+b	-	+b+p
	80 lU/ml in 10-ml vial,	+b	-	+b+p
	100 lU/ml in 10-ml vial	+b	-	+b+p
insulin zinc suspension	injection, 40 IU of insulin/ml in 10-ml vial	+b	o	+b+p
	80 IU of insulin/ml in 10-ml vial	+b	o	+b+p
insulin	100 IU of insulin/ml in 10-ml vial	+b	-	+b+p
(intermediate-acting) isophane insulin	injection, 40 IU of insulin/ml in 10-ml vial	+b	+b	+b+p
	80 IU of insulin/ml in 10-ml vial	+b	+b	+b+p
	100 IU of insulin/ml in 10-ml vial	+b	+b	+b+p

[1] *+: in vivo* studies required; +b: bioequivaience studies; +p: pharmacodynamic studies; +c: clinical trials; -: no *in vivo* studies required; *?:* decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp. 118-128.

Table 1 (continued)

Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
iodized oil	capsule, 200 mg	?	o	o
iopanoic acid	tablet, 500 mg	o	o	-
iron dextran	injection, 50 mg of Fe/ml in 2-ml ampoule	+c	-	+b+p
isoniazid	tablet, 100-300 mg +b	+b	-	
	tablet,100 mg + rifampicin, 150 mg	o	+b	+b
	150 mg + rifampicin, 300 mg	o	+b	+b
	tablet, 100 mg + thioacetazone, 50 mg	o	+b	o
	300 mg + thioacetazone, 150 mg	o	+b	o
isosorbide dinitrate	tablet (sublingual), 5 mg	+b	+b	+b
ivermectin	scored tablet, 6 mg o	+b	o	
ketoconazole	oral suspension, 100 mg/5 ml	+b	+b	+b
	tablet, 200 mg	+b	+b	+b
levamisole hydrochloride	tablet, 50 mg,150 mg	+b	+b	+b
levodopa	tablet, 100 mg + carbidopa, 10 mg	+b	+b	+b
	250 mg + carbidopa, 25 mg	+b	+b	+b
levonorgestrel	tablet, 150 µg + ethinylestradiol, 30 µg	+b	+b	+b
	250 µg + ethinylestradiol, 50 µg	+b	+b	+b
levothyroxine sodium	tablet, 50 µg,100 µg	?	+b	-
lithium carbonate	capsule, 300 mg	+b	+b	+b
	tablet, 300 mg	+b	+b	+b
mebendazole	chewable tablet, 100 mg	+b	+b	+b+c
medroxyprogesterone	injection, 150 mg/ml in 1 -ml vial,	?	+*b	+b
acetate (depot)	50 mg/ml in 3-ml vial	?	+*b	+b
mefloquine hydrochloride	tablet, 250 mg	+b	+b	+b
mercaptopurine	tablet, 50 mg +c+b	+b	+b	+b

[1] +: in vivo studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials;
-: no in vivo studies required; ?: decision on the type of in vivo studies pending; o: no information available, no final decision taken, or not available on national market. See also pp.118-128.

Table 1 (continued)

Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
methionine(DL-)	tablet, 250 mg	?	?	-
methotrexate sodium	tablet, 2.5 mg of methotrexate	+b+c	+b	+b
methyldopa	tablet, 250 mg	?	+b	+b
metoclopramide hydrochloride	tablet, 10 mg of metoclopramide	+b	-	+b
metrifonate	tablet, 100 mg	o	+b	o
metronidazole	suppository, 500 mg, 1 g	o	+b	o
	tablet, 200-500 mg +b	+b	+b	
metronidazole benzoate	oral suspension, 200 mg of metronidazole/5 ml	o	+b	o
mexenone	cream	o	+p+c	o
	lotion	o	+p+c	o
	gel	o	+p+c	o
miconazole nitrate	cream, 2%	+c	+p+c	+c
	ointment, 2%	+c	+p+c	+c
morphine sulfate	tablet, 10 mg	o	+b	-
nalidixic acid	tablet, 500 mg	+b	+b	+b
neomycin sulfate	ointment, 5 mg + bacitracin zinc, 500 IU/g	o	+p+c	-
neostigmine bromide	tablet, 15 mg	?	?	-
niclosamide	chewable tablet, 500 mg	o	+b	+b
nicotinamide	tablet, 50 mg	-	?	-
nifedipine	capsule, 10 mg	+b	+b	+b
	tablet, 10 mg	+b	+b	o
nifurtimox	tablet, 30 mg, 120 mg, 250 mg	o	+b	o
nitrofurantoin	tablet, 100 mg	?	+b	+b
norethisterone	tablet, 350 µg, 5 mg	+b	+b	o
	tablet, 1.0 mg +ethinylestradiol, 35 µg	+b	+b	o
norethisterone enantate	oily solution, 200 mg/ml in 1-ml ampoule	?	+b	o
nystatin	lozenge, 100 000 IU	+	?	+b
	tablet, 100 000 IU, 500 000 IU	o	-	-

[1] +: in vivo studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials;
-: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp.118-128.

Table 1 (continued)
Examples of national requirements for equivalence studies

Drug substance	Dosage form	Canada	Germany	USA
oxamniquine	capsule, 250 mg	o	+b	+b
oxybenzone	cream	-	+p+c	+c
	gel	-	+p+c	+c
	lotion	-	+p+c	+c
paracetamol	suppository, 100 mg	+b	-	o
	tablet, 100-500 mg	-	-	o
penicillamine	capsule, 250 mg	+b	-	+b
	tablet, 250 mg	+b	-	+b
permethrin	lotion, 1%	-	+p+c	+c
pethidine hydrochloride	tablet, 50 mg, 100 mg	o	+b	-
phenobarbital	tablet, 15-100 mg	-	o	-
phenoxymethyl-penicillin potassium	powder for oral suspension, 250 mg of phenoxymethyl penicillin/5 ml	o	+b	+b
	tablet, 250 mg of phenoxymethylpenicillin	?	+b	+b
phenytoin sodium	capsule, 25 mg, 100 mg	+b	+b	+b
	tablet, 25 mg,100 mg	+b	+b	o
phytomenadione	tablet, 10mg	+b	o	+b
pilocarpine hydrochloride	solution (eye drops), 2%, 4%	o	+p+c	-
pilocarpine nitrate	solution (eye drops), 2%, 4%	o	+p+c	o
piperazine adipate	tablet, 500 mg of piperazine	-	o	o
piperazine citrate	tablet, 500 mg of piperazine hydrate	-	o	+b
podophyllum resin	solution, topical, 10-25%	o	+p+c	-
potassium iodide	tablet, 60 mg	-	-	-
praziquantel	tablet, 150 mg, 600 mg	o	+b	+b
prednisolone	solution (eye drops), 0.5%	o	+p+c	o
	tablet, 1 mg, 5 mg	?	+b	+b
primaquine diphosphate	tablet, 7.5 mg of primaquine, 15 mg of primaquine	?	+b	-
procainamide hydrochloride	tablet, 250 mg, 500 mg	+b	+b	+b

[1] +*: in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials; -: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp.118-128.
Table 1 (continued)

Examples of national requirements for equivalence studies'

Drug substance	Dosage form	Canada	Germany	USA
procaine benzylpenicillin	powder for injection, 1 g (= 1 million IU),	?	-	+b
	3 g (= 3 million IU)	o	-	+b
procarbazine hydrochloride	capsule, 50 mg	+c+b	+b	+b
proquanil hydrochloride	tablet, 100 mg	o	+b	o
promethazine hydrochloride	tablet, 10 mg, 25 mg	?	+b	+b
propranolol hydrochloride	tablet, 10 mg, 20 mg 40 mg, 80 mg	+b	+b	+b
propyliodone	oily suspension, 500-600 mg/ml in 20-ml ampoule	o	o	-
propylthiouracil	tablet, 50 mg	?	-	+b
pyrantel embonate	oral suspension, 50 mg of pyrantel/ml	o	+b	+b
	chewable tablets, 250 mg of pyrantel	o	+b	o
pyrazinamide	tablet, 500 mg	+b	+b	+b
pyridostigmine bromide	tablet, 60 mg	+b	?	+b
pyridoxine hydrochloride	tablet, 25 mg	-	?	-
pyrimethamine	tablet, 25 mg + sulfadoxine, 500 mg	+b	+b	+b
quinidine sulfate	tablet, 200 mg	?	+b	+b
quinine bisulfate	tablet, 300 mg of quinine	+b	+b	-
quinine sulfate	tablet, 300 mg of quinine	?	+b	-
reserpine	tablet,100 µg. 250 µg	?	+b	+b
retinol palmitate	capsule, 200 000 IU (110 mg) of retinol	-	?	o
	sugar-coated tablet, 10 000 IU of retinol	-	?	o
riboflavin	tablet, 5 mg	-	?	-

[1]+: *in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials;
-: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp.118-128.

Table 1 (continued)
Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
rifampicin	capsule, 150mg, 300 mg	+b	+b	+b
	tablet,150 mg, 300 mg	+b	+b	+b
	tablet, 150 mg + isoniazid, 100 mg	o	+b	+b
	300 mg + isoniazid,150mg	o	+b	+b
salbutamol sulfate	inhalation (aerosol), 100 µg of salbutamol per dose	?,+p	+p+c	+p
	respirator solution for use in nebulizers, 5 mg/ml	?,+p	+p+c	
	tablet, 2 mg, 4 mg of salbutamol	+b	+b	+b
salicylic acid	cream, 3% + benzoic acid, 6%	-	+p+c	o
	ointment, 3% + benzoic acid, 6%	-	+p+c	-
	solution, topical, 5%	-	+p+c	o
silver nitrate	solution (eye drops), 1%	o	+p+c	-
silver sulfadiazine	cream, 1% in 500 g container	+c	+p+c	+c
sodium cromoglicate	inhalation, 20 mg/dose	?or+c	+p+c	+p+c
sodium fluoride	tablet, 500 µg	-	-	
sodium valproate	enteric coated tablet,	+b	+b	+b
	200 mg, 500 mg			
spironolactone	tablet, 25 mg	+b	+b	+b
sulfadimidine	tablet, 500 mg	o	+b	o
sulfadoxine	tablet, 500 mg + pyrimethamine, 25 mg	+b	+b	+b
sulfamethoxazole	oral suspension 200 mg + trimethoprim, 40 mg/5 ml	+b	+b	+b
	tablet, 100 mg + trimethoprim, 20 mg	+b	+b	+b
	400 mg + trimethoprim, 80 mg	+b	+b	+b
sulfasalazine	tablet, 500 mg	+b	+b	+b
tamoxifen citrate	tablet, 10 mg of tamoxifen,	+b	+b	+b
	20 mg of tamoxifen			
testosterone enantate	injection, 200 mg in	?	+b	-
	1-ml ampoule			
tetracaine hydrochloride	solution (eye drops), 0.5%	o	+p+c	-

[1] +: *in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials; -: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp.118-128.

Table 1 (continued)

Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
tetracycline hydrochloride	capsule, 250 mg	?	+b	+b
	tablet, 250 mg	?	+b	+b
	eye ointment, 1 %	? +p+c	-	
thiamine hydrochloride	tablet, 50 mg	-	?	-
thioacetazone	tablet, 50 mg + isoniazid, 100 mg	o	+b	+b
	150 mg + isoniazid, 300 mg	o	+b	o
tolbutamide	tablet, 500 mg	+b	+b	+b
trimethoprim	oral suspension, 40 mg + sulfamethoxazole, 200 mg/5 ml	+b	+b	+b
	tablet, 100 mg, 200 mg	+b	+b	+b
	tablet, 20 mg + sulfamethoxazole, 100 mg	+b	+b	+b
	80 mg + sulfamethoxazole, 400 mg	+b	+b	+b
tropicamide	solution (eye drops), 0.5%	o	+p+c	-
verapamil hydrochloride	tablet, 40 mg, 80 mg	+b	+b	+b
warfarin sodium	tablet 1 mg, 2 mg, 5 mg	?	+b	+b
zinc oxide	cream	-	+p+c	-
	ointment	-	+p+c	-

[1] +: *in vivo* studies required; +b: bioequivalence studies; +p: pharmacodynamic studies; +c: clinical trials
-: no *in vivo* studies required; ?: decision on the type of *in vivo* studies pending; o: no information available, no final decision taken, or not available on national market. See also pp. 118-128.

Reference

1. The use *of essential drugs. Sixth report of the WHO Expert Committee.* Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850).

Appendix 2
Explanation of symbols used in the design of bioequivalence studies in humans and commonly used pharmacokinetic abbreviations

C_{max}	The observed maximum or peak concentration of drug (or metabolite) in plasma, serum or whole blood.
C_{min}	Minimum plasma concentration.
C_{max}-ratio	The ratio of geometric means of the test and reference C_{max} values.
C_{av}	The average plasma concentration.
AUC	The area under the curve for drug (or metabolite) concentration in plasma (or serum or whole blood) against time. The AUC symbol may be qualified by a specific time (e.g., from zero to 12 hours, AUC_{12}).
AUC_t	AUC from zero to the last quantifiable concentration.
AUC_∞	AUC from zero to infinity, obtained by extrapolation.
AUC_τ	AUC over one dosing interval (τ) at steady-state.
AUC-ratio	The ratio of geometric means of the test and reference AUC values.
Ae	The cumulative urinary recovery of parent drug (or metabolite). The value of *Ae* may be that for a specific period, e.g., *Ae* from zero to 12 hours, Ae_{12}).
Ae_t	*Ae* from zero to last quantifiable concentration.
Ae_∞	*Ae* from zero to infinite time, obtained by extrapolation.
Ae_τ	*Ae* over one dosing interval at steady-state conditions.
d*Ae*/d*t*	The rate of urinary excretion rate of parent drug (or metabolite).
t_{max}	The time after administration of the drug at which C_{max} is observed.
t_{max}-diff	The difference of arithmetic means of the test and reference t_{max} values.
$t_{½}$	The plasma (serum, whole blood) half-life.
MRT	The mean residence time.
μ_T	Average bioavailabity of the test product.
μ_R	Average bioavailability of the reference product.

Appendix 3
Technical Aspects of Bioequivalence Statistics

The pharmacokinetic characteristics to be tested, the test procedure and the norms to be maintained should be specified beforehand in the protocol. A *post hoc* change of the methods specified for the statistical evaluation is acceptable only if adherence to the protocol would preclude a meaningful evaluation and if such change of procedure has been fully justified.

Concentration dependent data such as AUC and C_{max} should be log transformed prior to statistical analysis in order to satisfy the fundamental assumption of variance that effects in the model in an additive rather than a multiplicative manner.

Acceptance ranges for main characteristics

AUC-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 0.80-1.25 (see page 118). If therapeutic range is particularly narrow, the acceptance range may need to be reduced. A larger acceptance range may be acceptable if clinically appropriate.

C_{max}-ratio

This measure of relative bioavailability is inherently more variable than, for example, the AUC-ratio, and a wider acceptance range may be appropriate. The range used should be justified taking into account safety and efficacy considerations.

t_{max}-diff

Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs for a relation to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

Annex 4: Model Guidelines on Conflict of Interest and Model Proforma for a Signed Statement on Conflict of Interest

I. MODEL GUIDELINES ON CONFLICT OF INTEREST

A. Introduction

This document presents policy on "'conflict of interest" as it applies to external evaluators and members of advisory committees. These two categories of person are together referred to as "consultants" for the purposes of these guidelines.

A model proforma for a signed statement on conflict of interest is in Section II of this Annex.

B. Conflict of interest

Definitions and Principles

The common meaning of "conflict of interest" is a conflict between an individual's private or personal interest and his or her duty. However, it may also refer to a situation where an individual has several duties which conflict without involvement of any private or personal interests.

A conflicting private or personal interest may be financial or non-financial:

(a) When a decision-maker or consultant has a direct financial interest, however slight, in the matter to be decided, there is a conclusive presumption of bias and the decision-maker or consultant will thus be disqualified from acting.

(b) Where a decision-maker or consultant has a non-financial interest which gives rise to a reasonable presumption of bias, the decision-maker or consultant will be disqualified from acting. The test here is whether a reasonable observer would suspect that there is a possibility of bias, not whether that bias actually exists. A relevant non-financial interest may arise, for example, out of personal or family involvement between a decision-maker or consultant and a party whose interests are affected by the decision or recommendations. Such an interest may also arise where a decision-maker or consultant is seen to have prejudged the issues, either through preconceived opinions or prior involvement with the facts of a case on which he or she is required to make a decision on recommendations.

Conflict of interest in relation to consultants

There are variety of situations in which consultants may find themselves in a situation of conflict of interest between their professional activities (e.g. preparation of objective and independent evaluations, membership of independent committees) and personal and private interest (e.g. private consultancies, grants to cover travel and accommodation at company-sponsored conferences, share holdings, research grants, honoraria). It is recognized that almost all consultants have some *potential* conflict of interest because of their present or past association with the pharmaceutical industry.

Some situations of conflict of interest are clearcut and some are more difficult to determine. If an individual is an employee of, or a retained consultant to, a pharmaceutical company, there is a clear possibility of conflict of interest. If an individual is an employee of a government

organization, does no work on behalf of pharmaceutical companies, and is not in receipt of

gratuities or funding, there is minimal risk. Between these two situations is a spectrum of possibilities where the decision may be less obvious.

Contracts are unlikely to be offered to consultants in any one of categories 1 to 6:

1. The consultant works in the pharmaceutical industry, including pharmaceutical consultant companies, either as an employee or as an owner or part-owner (e.g. owner of a consultancy or shareholder in the pharmaceutical company).
2. The consultant receives a retainer (fee) from one or more pharmaceutical companies whose products she or he has to assess or which the new product is likely to replace.
3. The consultant has a *significant* direct current relationship with one or more companies. This may take the form of (a) financial support for an ongoing research project or projects (b), sponsorship of graduate or postgraduate students, or (c) company employees who are under the direct responsibility of the consultant.
4. He or she receives *substantial* financial assistance or *expensive* equipment to conduct research on behalf of the pharmaceutical company.
5. The consultant acts or has acted as a consultant for a pharmaceutical company *on the product she or he has agreed to assess*. Such a consultancy may include sponsorship as a speaker, or appointment as chairperson at professional meetings concerning the product, or attendance on behalf of the sponsoring company at national or international professional meetings concerning the product.
6. The consultant has had significant input to the planning or conduct of a clinical trial of the product, for example as a principal investigator, signatory to the study report, or author of any published or unpublished paper or other report of the study. Participation limited to the inclusion of patients in a large-scale multicentre study is *not* considered a significant conflict of interest.

A conflict of interest is less likely to be seen in situations 7 to 10:

7. The consultant has occasional contracts with one or more companies for particular projects, but does not have a significant relationship with any one company. She or he has not been directly involved with the product in question.
8. The consultant owns or works for a consultancy which does not provide advice to the pharmaceutical industry but may provide advice to other industries, such as the devices, food or paint industries.
9. The consultant occasionally provides advice to one or more companies on the design of clinical trials to be conducted prior to submission of an application for marketing authorization, but does not have a significant ongoing relationship with any one company (e.g. points 1 to 6 above).
10. The consultant has been invited to attend and contribute to national or international meetings organized by professional or academic associations.

The responsibility of consultants

A DRA cannot be aware of all of a consultant's involvements and their ramifications when a contract is offered. The onus is therefore on the consultant to declare in writing any potential conflict or what may be seen as a potential conflict to the DRA staff member who negotiated the contract or committee membership. If there is any doubt, the potential conflict must be declared.

The consultant may only proceed with the evaluation of the data or committee membership after any

potential conflict has been discussed with the DRA and found not to be significant.

For this reason, each evaluation contract requires the evaluator to sign a statement to the effect that she or he has no current conflict of interest and that, if the risk of such a conflict arises during the evaluation, the DRA will be notified immediately in writing.

The evaluator is expected to cease reading the application *immediately she or he becomes aware of a conflict of interest*, and return it promptly to the DRA.

C. Confidentiality

Any data concerning a company's product which are supplied by the DRA to a consultant for review are strictly confidential. As stated in the contract, all materials included in contract material must be accepted in strict confidence and held in safe and secure custody at all times. An application may be discussed only with DRA staff members.

Consultants must be aware of and avoid the possibility of indirect breaches of confidence. There is clearly a potential, consciously or subconsciously, to misuse information gained from a consultancy in other papers or scientific presentations on the product in question. Such a case would also constitute a conflict of interest. The consultant must not use information gained in this way in future scientific papers or presentations without the agreement of the company or individual who submitted the data.

D. Impartiality

To protect impartiality, the company concerned is not informed by the DRA of the consultant’s identity when applications, data or committee papers are forwarded to a consultant. For this reason, the consultant should have no direct communication with the company concerning the product. The consultant may not disclose his or her role to the company, even after a decision on the application has been completed.

E. Subcontracting the evaluation

A consultant is not allowed to subcontract part or all of an evaluation to any second person without written permission from the DRA. If the DRA agrees to such an arrangement, the consultant must ensure that the subcontractor is fully aware of the provisions on conflict of interest, confidentiality and impartiality set out in these notes.

If any part of an evaluation is subcontracted, the person who actually undertakes the work must also sign all reports to which she or he has contributed.

II. MODEL PROFORMA FOR A SIGNED STATEMENT ON CONFLICT OF INTEREST

It is not necessary for external evaluators to sign this proforma if they have signed the proforma external evaluation contract (see Annex 5) because the same declarations are included in the proforma contract.

I, ,

have agreed to participate in meetings of the committee known as

For the purposes of my membership of this committee, I declare as follows.

1. I do not hold any office, possess any financial or non-financial interest, or have any obligation whereby, directly or indirectly, duties or interests are or might be created which would conflict with my duties and interests as a member of this committee.

2. If, while participating in committee activities, either during a meeting or when reading or preparing papers for the committee, a conflict or an immediate risk of a conflict arises, I will immediately notify the [*name of regulatory authority*] of that risk and will cease the activity.

3. I will not disclose or make public any material which becomes available to me as a result of my membership of this committee, either during my membership or after my membership has ceased, without prior approval in writing from *[name of regulatory authority]*, except for information that is demonstrably in the public domain.

Name and address: .....

Signature: .....

Date: .....

Annex 5: Model Contract between a Regulatory Authority and an External Evaluator of Chemistry, Pharmaceutical and Bioavailability Data

This is a model contract between a drug regulatory authority (DRA) and an external evaluator of chemistry, pharmaceutical and bioavailability data, usually but not always in the context of an application for marketing authorization for a new pharmaceutical product. The sections in italics describe the general design of the contract and should not appear in the final version. Where an asterisk appears, the DRA should complete the section concerned for each individual contract before despatch to the evaluator.

[Name of drug regulatory authority]

CONDITIONS OF APPOINTMENT AS AN EVALUATOR OF CHEMISTRY, PHARMACEUTICAL AND BIOAVAILABILITY DATA ON A DRUG PRODUCT
*[*amend data types as applicable]*

Name of evaluator:*

Product:*

Applicant:*

Application No.:*

File reference No.:*

The conditions of appointment are :

1 (a) "Authority" means the *[name of drug regulatory authority]*;

(b) "Authority material" means all material supplied by the Authority to the evaluator in connection with, or relating, to this evaluation;

(c) "Contract material" means all material produced under this contract and includes reports, technical information, plans, charts, drawings, calculations, tables, schedules, printouts and data stored by any means.

2. All Authority material shall remain the property of the Authority. Upon completion by the evaluator of his/her evaluation or if requested by the Authority, the evaluator shall return all such material to the Authority.

3. Any intellectual property rights (including copyright) in contract material are owned by the Authority.

4. All materials supplied to the evaluator in connection with this evaluation are accepted in strict confidence and will be held in safe and secure custody at all times. The evaluator

accepts responsibility for the protection and maintenance of all contract material and Authority material supplied to the evaluator in connection with this evaluation.

5. The evaluator shall ensure that the contract material and Authority material are used, copied, supplied or reproduced only for the purposes of this contract.

6. The evaluator shall not disclose any contract material or Authority material concerning this evaluation, including the name of the applicant and the name of the product under evaluation, without prior approval in writing from the Authority.

7. The evaluator shall not communicate with the applicant, its employees or its agents with respect to the contract material or Authority material or any matter directly or indirectly related to the product under evaluation or the fact that she or he is undertaking an evaluation of one of that company's products.

8. The evaluator shall prepare a report following the guidelines supplied by the Authority but incorporating any information, facts or opinions that the evaluator feels to be important and relevant.

9. The evaluation is understood to include the evaluation of materials subsequently submitted in reply to matters raised by the evaluator. *[In the event that the applicant subsequently submits substantial additional data, the DRA may use its discretion as to payment of an additional fee to the evaluator.]*

10. The fee for the evaluation shall be *..... and payment will be made on completion of the satisfactorily prepared written report. *[May not be applicable if the external evaluator is an employee of the government, e.g. in a research institute.]*

11. In the event of discontinuance of the evaluation before completion through unavoidable circumstances, payment shall be made on a proportional basis for the sections completed.

12. The report shall be submitted to *[name and address of DRA]* and marked to the attention of *[responsible administrative staff member]* within *[... weeks]* of receipt of the data.

13. Both copies of this contract shall be signed by the evaluator upon receipt and prior to commencement of the evaluation. One copy shall be forwarded to the Authority immediately and the other retained by the evaluator.

14. If the evaluation is returned to the Authority within *..... weeks of receipt of the data, a bonus of *..... will be paid. *[This clause is optional . It is intended to encourage faster turn-round times. Experience has shown that quite small bonuses, e.g. 10% of the contracted fee, are sufficient to achieve rapid turn-round.]*

I agree to accept the general conditions of appointment as an evaluator of applications for marketing authorizations as outlined in the statements above, and I declare that:

(a) I do not hold any office, have any financial or non-financial interest, or have any obligation whereby, directly or indirectly, duties or interests are or might be created which would

conflict with my duties and interests under this contract.

(b) If, while performing the consultancy services specified above, a conflict or an immediate risk of a conflict arises, I will immediately notify the Authority in writing of that risk and will cease the evaluation.

Signature:

Name:
(Please print clearly)

Date:

Date documentation received:

Annex 6: Model Application Form for new Marketing Authorizations, Periodic Reviews and Variations, with Notes to the Applicant

This page comprises details of the application and is followed by a certification form concerning the data set . The remaining pages contain an index to the complete data set. The form and index should be read in conjunction with the Notes to the Applicant that follow. The glossary, list of abbreviations and references are as those appearing in the main text.

Marketing authorization No.: (only to be completed when a change to or review of the marketing authorization is required) **……**

A. Type of application (check the box applicable)

☐ New marketing authorization for a pharmaceutical product

☐ Periodic review of an existing marketing authorization

☐ Variation to an existing marketing authorization

B. Identity of the product

Proprietary name (trade name)
Approved generic name(s) (use the INN, if any)
Strength(s) per dosage unit
Dosage form
Route of administration
Anatomical therapeutic classification

C. Applicant

Name
Business address

Postal address
Telephone number . . . . . .Fax number. . . . .

D. Contact person in applicant company

Name:
Position in company: .
Postal address
Telephone number.. . . . . Fax number
E-mail address. .

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I the undersigned certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)
Approved generic name(s) (use the INN, if any)
Strength(s) per dosage unit
Dosage form
Applicant company

is correct and true, and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO guideline on "Good manufacturing practices for pharmaceutical products" Guideline 1 below, or an equivalent national guideline, is applied in full in all premises involved in the manufacture of this product.

2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.

3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.

4. Each batch of all starting materials is either tested or certified (in an accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications *before it is released for manufacturing purposes.*

5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.

6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.

7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications *before it is released for manufacturing purposes.*

8. Each batch of the finished product is either tested, or certified (in an accompanying certificate of analysis for that batch), against the full specifications in the accompanying documentation and complies fully with the release specifications *before it is released for sale.*

9. The person releasing the product for sale is an authorized person as defined by the WHO guideline "Good manufacturing practices: Authorized person - the role, functions and training" (Guideline 10 below).

10. The procedures for control of the finished product have been validated for this formulation.

The assay method has been validated for accuracy, precision, specificity and linearity.

11. The following WHO-type certificates are attached:

All aspects of the product which is the subject of this application are identical to that marketed in *[the country or countries issuing the WHO-type certificate(s)]*, including formulation, method and sites of manufacture, sources of active and excipient starting materials, quality control of the product and starting materials, packaging, shelf-life and product information (apart from language), except as follows:

(Append additional pages if necessary).

12. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.

13. The market authorization holder has a standard operating procedure for handling batch recalls of its products (Guideline 1 below, Part 7).

14. All the documentation referred to in this certificate is available for review during a GMP inspection.

15. Any clinical trials were conducted according to WHO's "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products" (*16*).

Signature

Name (print or type)

Position in company (print or type) .

Date: .

INDEX TO THE INFORMATION REQUIRED AND DATA SET	*Page*

Details of the product Route(s) of administration Visual description of the product Visual description of the packaging Proposed restrictions on sale or distribution. Choose the highest applicable classification in this order: - Scheduled narcotic; - Restricted prescription-only distribution (specify, for example, hospitals only); - Prescription only; - Pharmacy only; - Over-the-counter (OTC).	
Regulatory situation in other countries Provide a list of the countries in which this product has been granted a marketing authorization. State for each: • The restrictions on sale or distribution (as defined above but with additional comments as necessary); • Dosage form(s) and strengths; • Container/closure system. List all countries where the product has been withdrawn from the market, or where an application for marketing has been rejected, deferred or withdrawn. State the reason in each case.	
Properties of the active pharmaceutical ingredient(s) Provide at least the following information: • Chemical structure; • If relevant, the isomeric nature of the active ingredient, including stereochemical configuration (e.g. racemate, pure (*S*)-isomer, 50/50 mixture of (*Z*)- and (E)- isomers); • The solubility of the active ingredient in water at 25 or 37°C; • The solubility of the active ingredient in other solvents, such as ether, ethanol, acetone, and buffers of different pH (if the active ingredient is acidic or basic); • Other relevant physicochemical characteristics of the active ingredient, such as partition coefficient (usually octanol/water) and the existence of polymorphs; • Copies of infrared, nuclear magnetic resonance (proton and C-13), ultra-violet and mass spectra; • Information on the chemical stability of the API, and on physicochemical stability if relevant (e.g. formation of a hydrate, change of polymorphic form).	
Sites of manufacture - Active pharmaceutical ingredient(s) State the name and street address of each facility where manufacture (synthesis, production) occurs. Include any alternative manufacturers. For domestic sites, attach a copy of the current site licence issued by this drug regulatory authority. For each foreign site, attach a certificate issued by the competent authority in terms of Guideline 3 below. It may contain, as attachments, copies of GMP certification for other sites.	

Route(s) of synthesis of active pharmaceutical ingredient(s) (This information may not be available if the API is purchased via an intermediary instead of directly from the producer, in which case the manufacturer of the finished product should conduct a full set of tests on each batch.) Provide details of the route of synthesis for each active pharmaceutical ingredient, including reagents and reaction conditions. Provide specifications for starting materials, reagents and intermediates in the synthesis. Comment on likely synthetic by-products and degradation products, and discuss the results in the certificates of analysis for each site and method of manufacture. If available, provide a European certificate of suitability (*17* and *28*) with any appendices and the accompanying "Report A". In this case, only an outline of the route of synthesis is needed.	
Specifications for the active pharmaceutical ingredient(s) Provide a list of tests and limits for results for the API. Include test methods in sufficient detail for them to be replicated by another laboratory. Provide the results of validation of the methods for assay of the API and of impurities. If the ingredient is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced but not duplicated in the monograph. Provide details of any specifications additional to those in the pharmacopoeia. Provide certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.	
Stability testing of the active pharmaceutical ingredient(s) Provide the results of stability testing of the active pharmaceutical ingredient. Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities and assay (*14*), and for other tests as necessary (e.g. particle size testing). If the API is well established, studies should be conducted according to the principles outlined in the relevant WHO Guidelines (Guideline 4 below). For new active ingredient and products, see the relevant ICH guideline *(18).* Results should be included for physical as well as chemical tests, e.g., (where relevant) particle size and polymorphic form. The study should be designed to show whether trends in stability occur over time. State the proposed shelf-life (or retest date) and justify it in terms of the results of stability testing and the labelled storage conditions.	

Formulation Provide the formulation for a typical batch *and* for an administration unit, e.g. one tablet, 5 ml of oral solution, or the contents of an ampoule or bag of large volume parenteral solution, etc. Include excipients that may be removed during processing (e.g. solvents), those that may not be added to every batch (e.g. acid and alkali for pH adjustment), and the qualitative and quantitative composition of any tablet coating, capsule shell and inked imprint on the dosage form. State any overages. State the function(s) of each excipient (e.g. antioxidant, lubricant, binder). Indicate any substances whose content may be varied (e.g. inked imprint, tablet coating) and state how the content is decided for each batch (e.g. "The active therapeutic ingredient is adjusted for water content to a constant dry weight content; the content of maize starch may be varied by up to +25% depending on manufacturing conditions"). Provide either validation data or a rationale to justify ranges in the content of excipients. Ranges should not be excessive nor should they be automatic (e.g. "All excipients may be varied by ± 10%").	
Sites of manufacture - Finished product State the name and street address of each facility where *any aspect of* manufacture occurs, including production, sterilization, packaging and quality control. Indicate the activity performed at each site. Include any alternative manufacturers. For domestic sites, attach a copy of the current site licence issued by this drug regulatory authority. For each foreign site where the major production step(s) is/are carried out, attach a certificate issued by the competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Guideline 2 below). Include the product information approved by that authority with, if available, the summary basis of approval (or similar) and any other material that the authority deemed relevant (Guideline 2, section 4.7).	
Manufacturing procedure for the finished product Provide an outline of the manufacturing procedure for the finished product, including packaging. Provide a copy of the master formula and a copy of a manufacturing record for a real batch. The master formula should include information listed in Guideline 1, section 14.23.	
Specifications for excipients Provide a list of tests and limits for results for each excipient, including solvents, liquids to adjust pH, coatings, capsule shell, and inked imprint (on the dosage form). Include test methods in sufficient detail for them to be replicated by another laboratory. If the ingredient is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced but not duplicated in the monograph. Provide details of any specifications additional to those in the pharmacopoeia. Include microbiological limits for materials of natural origin. Only colours permitted by the EU's "List of permitted food colours", the FDA's "Inactive ingredient guide" or "Japanese Pharmaceutical Excipients" may be used *(19-22*).	

Specifications for the finished product Provide a list of tests and limits for results for the finished product, including sufficient detail of test methods for them to be replicated by another laboratory. If the product is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced but not duplicated in the monograph. Provide details of any specifications additional to those in the pharmacopoeia. Provide both release and expiry limits for results. Provide the results of validation of the assay method for this formulation. For pharmacopoeial methods, provide data which demonstrate that the method is applicable to this formulation.	
Container/closure system(s) and other packaging Give a detailed description of the container/closure system(s), including any liner or wadding, and provide details of the composition of each component. Describe other (e.g. outer) packaging, and state what materials they are made from. Provide the specifications for any part of the container/closure system(s) which comes into contact with the product or is protective. For parenteral products, components that will at any stage come into contact with any part of the product must comply with requirements specified by the BP, EP, JP or USP.	
Stability testing of the finished product Provide the results of stability testing of the formulation in each of the proposed marketing packs. Results of testing related formulations and/or the same formulation in other packaging may be provided as supporting information, but there must be at least some data on the product as it is. Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities and assay (*14*), and for other tests as necessary (e.g. particle size testing). If the product is a well established drug in an immediate release dosage form, studies should be conducted according to the principles outlined in the relevant WHO guidelines (Guideline 4 below). For new active ingredient and products, see the relevant ICH guidelines (*18*). For most types of product, results should be included for physical as well as chemical tests, e.g. (where relevant) the presence of particles in a solution and the dissolution rate of solid oral dosage forms. The study should be designed to show whether trends in the properties of the products are confirmed over time. State the proposed shelf-life and justify it in terms of the results of stability testing, the difference between release and expiry specifications, and the labelled storage conditions. Data should also be provided on the product's stability during any processing prior to use that may be recommended on the label or in product information, such as reconstitution of a powder, dilution of an injection, or dispersion of a tablet.	

Container labelling Labelling should include at least the items listed in Guideline 1 below, section 14.11, namely: (a) The name of the product; (b) A list of the active ingredients (using INNs if applicable - Guideline 8 below), showing the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume; (c) The batch number assigned by the manufacturer; (d) The expiry date in an uncoded form; (e) Any special storage conditions or handling precautions that may be necessary; (f) Directions for use, and any warnings or precautions that may be necessary; (g) The name and address of the manufacturer, company or person responsible for placing the product on the market; (h) The names of any excipients known to be a safety concern for some patients, e.g. gluten, metabisulfite, parabens, ethanol, or tartrazine. The labelled storage conditions should be achievable in practice in the distribution network. For containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container need only contain items (b),(c), (d), (g) - or a logo that unambiguously identifies the company - and the name of the dosage form or the route of administration.	
Summary of pharmacology, toxicology and efficacy of the product For each of the following types of application, provide full information on safety and efficacy as defined in guidelines by the European Union, the US Food and Drug Administration, or the Japanese Ministry of Health and Welfare: new active ingredients, new indications, new patient populations, other amendments to product information, new routes of administration, new dosage forms, all modified-release dosage forms, and new combinations of active ingredients. Note that a complete data set of the type expected for a new API is not usually required when the same API is already available on the same market, e.g. in a different dosage form. Supply at least the data required by the guidelines named above, e.g. for a modified release product. As an alternative to providing the full data set, it is acceptable to provide a WHO-type certificate issued by the competent authority (Guideline 2 below). As recommended in Guideline 2, the certificate should be accompanied by the product information and any patient information leaflet(s) as approved in the country issuing the certificate. A full data set on *quality* is required even when a WHO-type certificate is provided. Where (1) the new product is an alternative brand of an existing product (same active ingredient, dosage form and strength) or (2) a WHO-type certificate is provided instead of full data on safety and efficacy, provide, for the information of the DRA, a summary of toxicological, pharmacological and clinical information on each API. This should be based on the scientific literature and fully referenced. Copies of key texts should be attached. Published literature reviews in refereed journals are particularly helpful. The cited literature should relate as closely as possible to the product for which the application is submitted, for example in terms of the intended route of administration, patient population, indications etc. Include recent publications if possible.	

Interchangeability Discuss the interchangeability of the product with existing brands in this market, using Guideline 5 below as a basis. Include reference to quality, stability, therapeutic equivalence, product information and labelling. Discuss the sensitizing potential of excipients in the new formulation. Provide data on therapeutic equivalence as necessary.	
Product information Provide the draft product information based on WHO's "sample product information sheet" (Guideline 6 below, p.15-16). Provide copies of the approved product information in other countries, where available. (If available in more than five countries, provide only the product information for two key countries.) Where a monograph exists in either WHO Model Prescribing Information or the national or WHO model formulary, product information should usually include all the information in that monograph, provided that it is appropriate to circumstances prevailing in the Member State. Information on adverse reactions should conform to CIOMS guidelines (Guideline 7 below). Product information should not allude to unapproved indications, nor should it be speculative. Favourable comparisons with other products will only be permitted if there is a sound basis, for example in the literature. Note that it will be a condition of marketing authorization that all promotion of the product be consistent with the product information once the content has been agreed) and with Guideline 6.	
Patient information and package inserts Provide copies of all package inserts and any information intended for distribution with the product to the patient. These should be consistent with the product information and should comply with Guideline 6.	
Justification for any differences to the product in the country or countries issuing the submitted WHO-type certificate(s) When there are differences between the product for which this application is submitted and that marketed in the country or countries which provided WHO-type certificate(s), provide arguments and/or data to support the applicability of the certificates despite the differences. Depending on the case, it may be necessary to provide validation data for differences in site of manufacture, specifications, formulation, etc. Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.	

NOTES TO THE APPLICANT

1. The application form is suitable for applications for a new marketing authorization for a pharmaceutical product, to review an existing marketing authorization, or to vary an existing marketing authorization.

2. For definitions of terms, see the glossary.

3. Note that a number of WHO guideline documents exist and should be followed. A list of the guidelines follows these notes.

4. *New marketing authorizations*. For a new marketing authorization, provide all the data mentioned in the "Index to the complete data set" above.

5. *Variations*. To vary an existing marketing authorization, not all of the data mentioned in the "Index to the complete data set" are necessarily required. Provide:
   - A full description of the proposed change. Compare the product before and after the change, e.g. the nature of a changed component of the container and its nature before the change.
   - Validation data as necessary stability data, comparative dissolution data for a change to formulation, etc.).

   Include this statement in the letter of application:
   "I provide assurance that no changes have been made to this product other than (1) those which are the subject of this application and (2) changes described by *[name of DRA]* as not needing prior approval."

6. *Periodic reviews*. The intention of a periodic review is to consolidate the information held by the DRA. Any pharmaceutical (manufacturing, quality control, shelf-life, container labelling, etc.) variations/changes made to the product since the first marketing authorization or the last review should be either those for which prior approval has been obtained or those not requiring prior approval. Any safety updates should have been made when the relevant safety information became sufficiently well established as defined by CIOMS (Guideline 7, p.39). GMP practices should have been maintained and, as necessary, improved at all sites of manufacture.

For the periodic review of an existing marketing authorization, submit the following information:

(a) An updated WHO-type product certificate for each foreign site of manufacture of the finished product (Guideline 2, section 3.5). *When the draft WHO guidelines for certification of APIs have been finalized (Guideline 3), it may also be necessary to supply WHO-type API certificates for sites of manufacture of APIs.*
(b) Updated certificates of GMP for domestic manufacturing sites.
(c) A chronological list of all approved pharmaceutical variations of any type, and all amendments made to product information since the first marketing authorization or the last periodic review. Provide the dates of approval and file reference for each change;
(d) A set of current specifications for the API(s) and finished product, including test methods in sufficient detail for them to be replicated by another laboratory.

The periodic review should not be used as an opportunity to seek authorization for new variations. These should be the subject of separate applications. Nor should it be a means of regularizing unauthorized changes to pharmaceutical or product information.

7. In product information, promotional activities and applications, always use an INN name for the

generic name when one exists (Guideline 8).

8. “ATC classification” means the WHO Anatomic Therapeutic Chemical classification and “DDD” means the WHO Defined Daily Dose (Guideline 9).

9. Where an applicant is asked to “justify” or “provide a justification”, it is intended that scientific information and/or logical argument be provided.

10. The following pharmacopoeias are recognized for the purposes of this application form.

- .....
- .....
- .....

11. References to a pharmacopoeia should normally be to the current edition. An applicant must justify citing an edition other than the latest. If there is no monograph in the current edition, the year of the most recent monograph should be cited.

12. The European Pharmacopoeia Commission will, upon submission of a full drug master file (*15*) concerning production of an API by a particular synthetic route at a particular site, determine whether or not the relevant EP monograph is suitable to control the material fully. If the monograph is suitable, the Commission will issue a “certificate of suitability” (*17* and *28*). Some certificates of suitability have appendices, and these must be attached. The accompanying “Report A” is available to the manufacturer on request.

GUIDELINES APPLICANTS SHOULD CONSULT

Guidelines marked with an asterisk are also available as part of a compendium entitled "Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, Volume 1". (Geneva, World Health Organization, 1997)

Guideline 1
Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992:14-79 (WHO Technical Report Series, No. 823).

Guideline 2*
Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996: 155-177 (WHO Technical Report Series, No. 863).

Guideline 3
WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Proposed guidelines for the certification of active pharmaceutical ingredients. Geneva, World Health Organization, 1997 (document WHO/PHARM/96.586 Rev.1).

Guideline 4*
Agreement Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996: 65-79 (WHO Technical Report Series, No. 863).

Guideline 5*
Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996: 114-154 (WHO Technical Report Series, No. 863).

Guideline 6
Ethical criteria for medicinal drug promotion. Geneva, World Health Organization, 1988.

Guideline 7
Guidelines for preparing core clinical-safety information on drugs. Report by the Council for International Organizations of Medical Sciences (CIOMS). Geneva, World Health Organization, 1995.

Guideline 8
Guidelines on the use of International Nonproprietary Names (INNs) for Pharmaceutical Substances. Geneva, World Health Organization, 1997 document (WHO/PHARM S/NOM 1570).

Guideline 9
Guidelines for ATC classification and DDD assignment. Oslo, WHO Collaborating Centre for Drug Statistics and Methodology, 1996.

Guideline 10
Good manufacturing practices: authorized person - the role, functions and training. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1998: (WHO Technical Report Series, No.885). (in print)

Annex 7: Detailed Advice on Evaluation of Data by the Drug Regulatory Authority

This Annex contains detailed advice on a number of miscellaneous points that are likely to arise during the evaluation process. It is not a complete checklist of points to consider. Advice already included in the main text of the manual is not repeated here. The glossary, abbreviations, references and annexes are as those appearing in the main text.

When consulting this Annex, DRAs may fin it useful to refer to the decision tree for marketing authorizations using WHO-type product certificates appearing in Part IV of the manual, under "Evaluation of data on quality".

1. WHO-type certificates of pharmaceutical product (WHO-type certificates)
2. Quality control tests and limits
3. Identity of active ingredient
4. Impurities in the API
5. Assay of APIs
6. Physicochemical properties of APIs
7. Quality of excipients
8. Assays of active ingredients in finished products
9. Testing for impurities in the finished product
10. Tests on the finished product
11. Stability
12. Assay methodology
13. Container labelling
14. Trade names
15. Product information (PI)
16. Interchangeability
17. Papers to be presented to the Expert advisory body for a decision on a multisource pharmaceutical product
18. Variations
19. Periodic reviews of marketing authorizations

1. WHO-type Certificates of Pharmaceutical Product (WHO-type certificates)

It should be noted that "Requests for provision of certificates offering more limited attestations - for instance, that the manufacturer complies with GMP or that the product is authorized for "free sale" within the country of export - are discouraged" (Annex 2, section 3.2).

What the certificate means

If the exporting country has *not* authorized the product to be placed on its own market the WHO-type certificate amounts to certification of the manufacturing standard at the site in question. Neither an officially approved product information nor an evaluation report will be available.

If the exporting country *has* authorized the product to be placed on its own market,
the WHO-type certificate, in addition to certifying the manufacturing standard at the site in question, implies that the country issuing the certificate accepts that the product is of adequate quality, safety and efficacy to remain on its own market. Therefore an officially approved product information document, such as the European summary of product characteristics, should normally accompany the

certificate (Annex 2, Appendix 1, 2A.5). If this document is not available, then the product is probably "grandfathered" (see glossary) and has not been fully evaluated. Some countries also issue a summary basis of approval that summarizes the technical basis on which the product has been authorized.. When this is available, it should also be attached to the certificate (Annex 2, Appendix 1, 2A.4).

Where a WHO-type certificate is issued and the product has marketing authorization in the issuing country, it is not necessary to seek separate certification of the sites of manufacture of the API.

If the product is not identical to that in the issuing country, the model application form (Annex 6) allows applicants to list any differences (under "Certification by a responsible person in the applicant company") and to justify the differences (under "justification for any differences to the product in the country or countries issuing the submitted WHO-type certificates"). DRAs must then decide whether the differences are minor and have been adequately justified, and consequently whether the WHO-type certificate is relevant.

More than one country of manufacture

Manufacture of a single product may occur in more than one country, for example in the following circumstances.

(a) Different phases of manufacture may be conducted in different countries. For example, a batch of tablets may be prepared in bulk in country A, and packaged and subjected to quality control testing in country B.
(b) The product may be *fully* manufactured in both countries A and B, and the applicant wishes to obtain approval to use both sites of manufacture.

The WHO-type certificate should normally be prepared by the country that directly exports the product to the importing country, i.e. country B in example (a) above. If the product has marketing authorization in this exporting country and the product to be imported is identical to that authorized, the sites of manufacture in third countries will have been approved by the exporting country. In that case, no further review of GMP in third countries is necessary. Indeed, some exporting countries might voluntarily attach a GMP certificate for sites in other countries (Annex 2, Appendix 1, explanatory note 16).

If the exporting country has not authorized the product to be placed on its own market, the importing country may seek WHO-type certificates from more than one country, i.e. countries A and B in the above examples.

In example (b), both countries can separately be asked for a WHO-type certificate.

Currency and validity

The WHO Certification Scheme recommends that the exporting country prepare a separate certificate to be made available for each importing country, and that certificates should reflect any variations made to marketing authorizations (Annex 2, section 3.5). Consequently, certificates should always be current (recent) and each DRA may wish to define what it considers to be "current". If there is any doubt as to the status or validity of a certificate, the DRA should request an identical copy, clearly marked as duplicate, directly from the certifying authority (Annex 2, section 4.9).

If there is doubt that the authority issuing a WHO-type certificate satisfies the prerequisites for the scheme, there is a provision (see Annex 2, section 2.5) which reads:

> "Each Member State assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision for external inspection or assessment under any circumstances, either of a competent national authority or of a manufacturing facility. However, should a Member State so wish, it can approach WHO, or a well recognized drug regulatory authority, occasionally to delegate consultants to act as advisers in the course of both national inspections and inspector training activities."

DRAs may wish to prepare a list of Member States from whom WHO-type certificates are considered acceptable, perhaps in conjunction with other authorities with which it collaborates. Any such list should be kept up to date.

The source of the certificate

All requests for WHO-type certificates should be channelled through the agent (applicant) in the importing country (Annex 2, section 3.6).

2. Quality control tests and limits

Tests and limits for the API and the finished product should, as a minimum, comply with relevant pharmacopoeial requirements, including general requirements such as those in the International Pharmacopoeia (IP) for parenteral preparations, capsules, and so forth. Additional tests and limits may be necessary, for example for the dissolution rate of solid dosage forms of water-insoluble active ingredients when the pharmacopoeia does not include a test. Examples might be amoxicillin capsules and primidone tablets.

Pharmacopoeias sometimes do not set limits because they are not necessary for all products. An example is the particle size of a water-insoluble API. It is not appropriate for the pharmacopoeia to set a limit because suitable limits may vary with the use to which the starting material is put. If the API is present in the product as solid particles and does not go into solution during manufacture, a limit on particle size would normally be appropriate. But the same material may be used to manufacture a solution, for which a particle size would be irrelevant. For example haloperidol has a solubility in water of less than 0.001% (BP 1998). It would be appropriate to include limits on the particle size range of API used to manufacture haloperidol tablets because the drug is present as a solid and does not go into solution during manufacture. The particle size range may well effect bioavailability. However the same API is in solution in Strong Haloperidol Solution BP, and particle size limits would not be needed for API used in its manufacture.

When a product is given marketing authorization, and the specifications include compliance with a pharmacopoeial monograph, it is usual to allow automatic updates as new editions of the same monograph are published in the same pharmacopoeia. Any tests additional to those of the pharmacopoeia must continue to be applied, such as particle size and limit tests for impurities relevant to a particular synthetic route.

3. Identity of active ingredient

There should be a test (or tests) in quality control of the API to ensure that it is the intended

substance. Some active ingredients are available either as a single enantiomer, as a racemate (e.g. dexamfetamine and amfetamine), or as multiple isomers (e.g. labetalol), in which case it is necessary to ensure that the active ingredient is the same from batch to batch (in the case of labetalol, the ratio of the two pairs of racemates should be controlled). The salt form and/or state of solvation may also need to be controlled, e.g. amoxicillin sodium versus amoxicillin trihydrate. Control of the ratio of (E)- and (Z)- isomers (*cis*- and *trans*-) may be necessary for older active ingredients such as clomifene.

Test procedures for identity should be validated (*14*).

4. Impurities in the API

For many, but not all, existing multisource pharmaceutical products, data on safety of the API are available from toxicological and clinical studies. At the very least, the fact that the comparator has been marketed for some time is assumed to provide *de facto* evidence of lack of major toxicity. This is an assumption and may not be valid in all circumstances, such as when the product is marketed only in countries where there is no effective adverse reaction monitoring system.

Accepting this limitation, to be able to consider that information on the safety and efficacy of established products is applicable to new multisource pharmaceutical products the impurity content of the new brand must be no greater than that of the comparator. Quantitative limits on individual impurities in the API must be no greater than those for the comparator, and ideally there should be no new impurities in the new brand. If these conditions do not hold, then strictly speaking new safety studies should be considered.

To make the necessary comparison of impurity content, ideally the limits on impurities in the comparator product should be known, together with information as to what impurities are actually found. The impurities actually found may not be detected or controlled by the methods and limits in pharmacopoeias, so that additional controls are sometimes necessary. Unfortunately, information on impurities actually found in the comparator is often not available to the DRA because the comparator began to be marketed before premarket assessment was introduced. To seek information on impurities in the comparator in order to be able to assess the new brand may not be considered equitable in all jurisdictions, but some may consider it justifiable on grounds of public safety. A complete assessment of the appropriateness of impurity limits also requires information on the route of synthesis, and the opinion of an experienced organic chemist as to what by-products are likely following synthesis by that particular route. It is then possible to assess whether the possible by-products are likely to be detected by the proposed methodology for impurity testing. There should be a similar assessment of likely routes of degradation and whether the likely degradation products will be detected by the proposed impurity testing.

European certificates of suitability

The European Pharmacopoeia (EP) Secretariat will, upon submission of a dossier (*15*) concerning production of an API by a particular synthetic route at a particular site, determine whether or not the relevant EP monograph is suitable to control the purity of the API (*17* and *28*). If the secretariat decides that the monograph is suitable, a certificate of suitability is issued. If the monograph is not able fully to control the purity of the API, the necessary additional tests will be mentioned on the certificate and appended to it. If the API is not yet used in medicinal products in Europe, any impurity above 0.1% must be "qualified", that is, compared to those listed in the monograph and, if new, identified as such or compared to the impurity profile of APIs already on the market in Europe. If relevant, applicants must include information on the potential toxicity of impurities.

Such certificates can therefore apply the standard of the least acceptable product in Europe. However, a company that obtains a certificate of suitability is also entitled to request a copy of the EP Commission's evaluation of the data set ("Report A"). If DRAs request this report from the company, they can ascertain the basis on which the certificate of suitability was issued before accepting it. A useful feature of EP certificates of suitability is that a manufacturer must agree to be inspected by a relevant authority.

Therefore, DRAs should ensure that European certificates of suitability are accompanied by (1) any appendices mentioned on the certificate and (2) Report A.

By far the most desirable situation is for the API to be controlled by tests and limits that have been shown to be suitable for the particular synthetic route and site of synthesis. This is achieved in countries that have well resourced agencies. However, it is recognized that this outcome may not at present be achievable by all DRAs, for two reasons:

(1) The DRA may decide that its resources do not permit assessments in this detail.

(2) The reality at the present time is that batches of pharmaceutical starting materials pass through multiple hands, so that their origin and route of synthesis becomes obscure. Purchase from intermediaries is not recommended (*13*), but it is recognized that it occurs in some circumstances, for example when price is a factor in determining accessibility. It is emphasized that this is not a desirable situation.

In both these situations, smaller DRAs may decide to rely upon compliance of an API with the impurity requirements of a pharmacopoeia. In that case, the following is recommended:

- The latest edition of the pharmacopoeia should be specified so as to take advantage of the most up-to-date information available on important properties of starting materials, especially in relation to contaminants, and on testing methodology.
- Each batch of API should be *fully* tested for compliance with specifications by the finished product manufacturer.
- A confirmatory certificate of analysis from the supplier should be available for each batch, and the certificate should be satisfactory as defined in WHO's GMP guidelines (*13* p.57).

The WHO draft guideline for the certification of APIs, which seeks GMP certification of all sites of manufacture of APIs, will, once enforced worldwide, be a major step in achieving better control.

5. Assay of APIs

Assay procedures for APIs should if possible be specific for the API in the presence of impurities. However, this may not be essential if the remainder of the monograph fully controls the content of all types of impurity, including as necessary degradation products, synthetic by-products, heavy metals and non-combustible contamination.

6. Physicochemical properties of APIs

It may be necessary to control the physical properties of APIs, for example (as necessary) particle size and polymorphic form.

7. Quality of excipients

Information on the route of synthesis is less readily obtainable for excipients. Consequently, for reasons similar to those outlined for APIs, it is recommended that excipients comply with the latest edition of a pharmacopoeia, and that each batch obtained via an intermediary rather than directly from the producer be fully tested by the finished product manufacturer before use.

Only colours listed in the European Union's "List of permitted food colours", FDA's "Inactive ingredient guide" or the "Japanese Pharmaceutical Excipients" list (*19*-*22*) should be permitted.

8. Assays of active ingredients in finished products

Assay methodology in pharmacopoeias must be validated for each formulation. An example of what can go wrong is a formulation which, when processed by the pharmacopoeial method, produces a opalescent solution at a point at which ultra violet absorption is to be measured.

9. Testing for impurities in the finished product

If the DRA is convinced that a company is adequately ensuring the absence of significant synthetic by-products in the API, the company need not test for those by-products in the finished product. It is necessary, however, to test for impurities that may be breakdown products of the active ingredient.

The DRA may wish to test for synthetic by-products in the finished product as a part of its regulatory role in monitoring quality.

Test procedures for detecting and/or quantitating impurities should be validated (*14*).

10. Tests on the finished product

In addition to tests for identity and assay of API and for absence of impurities, it is often appropriate to conduct tests on the physicochemical properties of finished products. Examples

include particulate contamination of solutions for injection, lack of phase separation of emulsified injectables, and the particle size of suspensions.

11. Stability

Products must maintain their quality for the full length of the shelf-life when stored in the final marketing pack under any storage conditions permitted by the label. The permitted storage conditions must be attainable in local circumstances, for example in warehouses and distribution systems.

Products must also be stable when processed according to labelled instructions, such as during reconstitution or dilution.

12. Assay methodology

All assay methodology should have been validated. A number of suitable guidelines are available concerning validation of analytical procedures, for example those of ICH *(14)*.

13. Container labelling

In line with GMP guidelines (*13*), container labels should comply with national legislation and should include at least all of the following information:

- The name of the product;
- A list of the active ingredients (using INNs if applicable; *23*), showing the amount of each present, and a statement of the net contents, e.g. number of dosage units, weight or volume;
- The batch number assigned by the manufacturer;
- The expiry date in an uncoded form;
- Any special storage conditions or handling precautions that may be necessary;
- Directions for use, and any warnings or precautions that may be necessary;
- The name and address of the manufacturer or the company or the person responsible for placing the product on the market.

Some concession is appropriate for small containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton. If the outer pack bears all the required information, the immediate container need only contain items (b), (c), (d), (g) - or a logo that unambiguously identifies the company - and the name of the dosage form or the route of administration (see section on "Container labelling" in Annex 6).

14. Trade names

DRAs may or may not have the legal authority to approve proposed trade names, depending on national legislation. However, even if this function is not written explicitly into legislation, DRAs may nevertheless have the authority to disallow a trade name on the grounds that it constitutes a safety hazard or is misleading. Examples include names that imply unapproved claims, such as an unapproved:

- indication, e.g. "Bacta.....", or "Hypno.....";
- patient population, e.g. "Pregna.....", or "Infa....."; or
- dosage regimen, e.g. "Uni.....", or "Mono.....".

If a product's principal indication(s) is/are changed or there is a change in the API, it may be necessary to consider whether the trade name is still appropriate. For example if a product is indicated for angina and has the trade name "Cardioproduct", and later the principal indication is changed to claudication, the trade name would no longer be appropriate.

Names that are based on generic names, especially INNs, are also to be discouraged. The Forty-sixth

World Health Assembly in May 1993 requested Member States "to develop policy guidelines on the use and protection of international nonproprietary names, and to discourage the use of names derived from INNs (*23*), and particularly names including established INN stems as trade marks" (resolution WHA46.19). The request was based on a statement by the WHO Expert Committee on the Use of Essential Drugs (*5*) that use of a trade mark based on an INN, and particularly one based on an INN stem, "can frustrate the rational selection of further INNs for related substances, and it will ultimately compromise the safety of patients by promoting confusion in drug nomenclature".

15. Product information

Organization and content

Product information should normally be based on WHO's "Sample Product Information Sheet" (Annex 8, Appendix). Where a monograph exists in either WHO Model Prescribing Information or the model formulary, product information should usually include all the information in that monograph. Information on adverse reactions should conform to CIOMS guidelines (*24*). Product information should not allude to unapproved (off-label, undocumented) indications, nor should it be speculative. Favourable comparisons with other products should be avoided and only permitted if there is a sound clinical basis, documented in the literature, as such claims may later be used in promotion (see below).

A second, shorter version of product information may be appropriate for use in primary health care, and for this WHO's series entitled Model Prescribing Information (*25*) would be a suitable format. The product information itself may then be considered as a reference text which provides more in-depth information.

All promotion should be based on product information

It should be a condition of marketing authorization that all promotion of the product be consistent with the agreed product information and with WHO's guidelines on ethical criteria for Medicinal drug promotion (Annex 8, Appendix). Monitoring by a DRA of all promotion would be resource-intensive and is beyond the capacity of even well resourced authorities. Therefore the usual means of control is a system of random audits with suitable sanctions for breaches.

Note that the World Health Assembly has recently adopted a resolution on "Cross-border advertising, promotion and sale of medical products using the Internet" (*26*).

Product information should be consistent with the container labelling and with the product

The product information should be consistent with both the nature of the product and with container labelling. Examples of inconsistencies might include:

- The container label states that the product contains a particular steroid whereas the product information states that it contains the acetate ester of the steroid;
- The container label states that the product should be diluted before infusion, whereas the product information refers only to administration intravenously;
- The product information states that the product is not to be used in children, whereas the brand name on the container implies use in children;
- The product information refers to a dose of 25 mg when the product is a 50 mg capsule;
- The product information recommends a course of 5 ml twice daily for three days when the product contains only 25 ml of liquid.

Comparison with existing product information

It is not usually acceptable to have two marketing authorization holders of the same multisource product on the same market when their product information are inconsistent. Normally the evaluator should compare the product information for the new product with that of the comparator brand, carefully consider any differences, and determine whether amendments are necessary. In general, one or both of the product information will have to be amended so that they are not inconsistent and match as close as possible, although the wording need not be identical. Sources of information for this exercise should ideally be independent, reliable and complete, which may involve a literature search and review. In practice, reference is usually made to standard textbooks of medicine and pharmacology, national compendium of approved product information, and any existing national formulary. If a product information is available for the same product in another country, particularly one with a well resourced DRA, a copy should be sought for comparison. When a new API has recently come out of patent (for example in the last five years), the innovator's product information is normally a suitable starting point for a multisource product information.

Differences in product information may have to be tolerated in certain situations, particularly where local legislation allows new uses to be patented (new indications in the case of pharmaceuticals) or where market exclusivity arrangements apply.

It should be noted that not all existing product information meet current standards. Product information for older products in particular need careful scrutiny and in some cases may need to be substantially rewritten.

The advice of the expert advisory body is useful in finalizing product information, particularly to take advantage of expertise relating to local circumstances and endemic diseases.

Patient information or package inserts

Any patient information or package inserts should be consistent with the agreed product information and should comply with guidelines in WHO's *Ethical criteria for medicinal drug promotion* (see Annex 8).

16. Interchangeability

WHO's guideline on "Multisource (generic) pharmaceutical products" (Annex 3, Part One, section 2) mentions a number of features that are important to interchangeability:

- compliance with appropriate quality standards and at least compliance with relevant pharmacopoeial standards;
- stability;
- possible differences in sensitizing potential due to the use of different excipients;
- therapeutic equivalence in terms of, as appropriate, bioequivalence, pharmacodynamic studies, clinical studies or *in vitro* dissolution rate;
- product information and labelling.

Each of these features will be briefly examined in turn.

Quality

Various options for control of quality have been outlined earlier in the manual. There is no objection to a new multisource pharmaceutical product complying with a higher standard of quality than an existing product, but any difference in specifications should be considered carefully in terms of what effect it might have on interchangeability. For example, a faster *in vitro* dissolution rate may entail a difference in plasma concentration/time profile, which in turn could have therapeutic implications depending on the active ingredient and its indications. On the other hand, a narrower limit for the same impurities, or for assay of the active ingredient, implies a product of higher quality and it is difficult to envisage an adverse clinical consequence.

Stability

Stability should be examined as a part of the premarket evaluation of quality. Data should be available as described in WHO guidelines (see Annex 11). Different shelf-lives are acceptable for different brands of pharmaceutical equivalents as long as each is clearly labelled with the correct expiry date appropriate to that product and batch.

Different excipients

Different brands usually contain different excipients. Idiosyncratic reactions to excipients are difficult to eliminate completely, but can be minimized by avoiding excipients known to have a high incidence of such reactions. Information may be available in the published literature (*19*-*22*, *27* and *31*). Safety data should be sought for new excipients. Well resourced agencies may have already completed a scientific report on data on new excipients.

Therapeutic equivalence

Pharmaceutical equivalents on the same market should be interchangeable as defined in the WHO guidelines (see Annex 3). Interchangeability must therefore be considered during evaluation of applications for new products that are pharmaceutical equivalents of well established drugs on the same market. If there is a product on the same market that has been fully evaluated in terms of quality, safety and efficacy (often the innovator), it will be the most relevant comparator. However, some manufacturers market products with different characteristics in different countries (*12*). If the study of equivalence has compared the new product with a brand available on *another* market, the applicant should provide evidence which convincingly demonstrates the relevance of the study.

For some products, it is not essential for pharmaceutical equivalents to have exactly the same rate and extent of bioavailability. The definition of "bioequivalence" in Annex 3 allows for this:

> Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar
>
> dose, *are similar to such a degree that their effects can be expected to be essentially the same*. "[emphasis added]

When studies show that the bioavailability of a new product is not the same as that of the existing pharmaceutical equivalent, it will usually be appropriate to seek the advice of the expert advisory body as to whether the products can be designated bioequivalent.

Bioequivalence is difficult to establish for some products, such as slow-release formulations, and high precision is required for others, such as anticoagulants and anticonvulsants, which have a steep dose-

response curve and/or a low therapeutic index. Some DRAs simply declare this type of product "not interchangeable". But for countries with scarce resources and limited distribution facilities, it may be unrealistic to expect that the same brand will always be available for a particular patient. Advice from primary health care workers and pharmacists responsible for distribution of pharmaceuticals (e.g. those who are members of the expert advisory body) is important on this point. It is not an option simply to stipulate that only those products distributed to remote areas must be interchangeable because the appropriate studies would then be even less affordable in the more limited market. It may be appropriate to seek an opinion from the expert advisory body on the risks and benefits of permitting multiple brands to be made available in this situation before the DRA makes a decision.

In evaluating bioequivalence, evaluators should bear in mind the possibility that the existing (comparator) product may not have adequate bioavailability. If the area under the plasma concentration-time curve of the new brand is greater than that of the comparator, that may be either because the new product uses a different technology (such as absorption enhancers) or because the comparator is of poor quality. To achieve interchangeability, the DRA's options in the latter case are either to cancel the marketing authorization of the comparator or to require that generics mimic the comparator's plasma concentration-time curve. The decision should normally be in favour of the comparator unless it is clearly a poor product. (See also "Non-interchangeability" below)

It should be noted that a faster rate of absorption with the same area under the curve does not necessarily mean a better product. For example, fast absorption of carbamazepine and nifedipine has been shown to result in side-effects in at least some patients (*29, 30*). There is no substitute for careful and informed consideration of each case, after having fully reviewed the literature and consulted appropriate experts.

In the event that a DRA decides to cancel the marketing authorization of the existing product, it is essential that the change-over be carefully planned. Health professionals should be advised in advance so that they can take appropriate steps to monitor patients during the change-over period. The sponsor of the newly authorized product should issue suitable letters to prescribers and pharmacists. The text of all such letters should be agreed in advance with the DRA.

If, in assessing an application for a new product, the DRA intends to rely on a report or decision made by another authority, the question of interchangeability with a suitable locally marketed comparator must be considered. Therefore, even if the authority providing a report or WHO-type certificate considers that interchangeability has been adequately addressed, it should be *re*considered by the local DRA (i.e. for each market) because the comparator may be different. If the applicant can demonstrate to the DRA's satisfaction that the comparator is identical in the two countries, that may be sufficient assurance of bioequivalence. If the products are similar but

not identical, the applicant should provide argument and/or data to support interchangeability with the local comparator.

Product information and container labelling

As noted above, the product information of new products should be consistent with that of any existing brand.

It should be clear from the labelling of the new and existing brands that these are generic versions of the same multisource pharmaceutical product. This is achieved by use of generic names (INNs) in Product information and container labelling.

Non-interchangeability

If a study shows that two multisource products are *not* interchangeable, the DRA has three options:
1. Not to allow marketing of both products simultaneously;
2. To consider the second product to be a different dosage form; or
3. To allow simultaneous marketing of non-interchangeable products.

In the first case, the DRA would normally reject the second application. But, if the data show that the product already-marketed is of poor quality, there may occasionally be a case for approving the new product and withdrawing the authorization for the existing product. The change-over would have to be handled carefully, ensuring that the two products are not available simultaneously and warning prescribers and pharmacists in advance that patients must be monitored carefully during the transition (normally by means of letters to prescribers and pharmacists).

In the second case, the difference between the two products is so significant that they can be considered different dosage forms. This is an exceptional situation and should be avoided if possible because there will always be a chance of confusion between the products. If, for example, the new product has the same extent of absorption (area under the curve) in a bioequivalence study but is much more rapidly absorbed, it may be appropriate to consider it a "rapid absorption" or "prompt release" product. Clinical evidence would be needed to show that the product is safe and efficacious, for example that the higher maximum plasma concentration does not cause adverse effects, and that the (probably) lower trough plasma concentration does not lead to reduced efficacy. It would be essential to ensure that prescribers and pharmacists are aware that the products are different, and the new product should be given a different generic name, such as "..... rapid release tablets". The holder of the new market authorization would be responsible for ensuring that the market launch makes the difference very clear.

The third case is undesirable, particularly for countries with scarce resources and limited distribution facilities (see above under "Therapeutic equivalence").

17. Papers to be presented to the expert advisory body for a decision on a multisource pharmaceutical product

In considering an application for a new multisource pharmaceutical product, the expert advisory body must have sufficient information before it to be able to make a decision that is independent of both the applicant and the DRA. Papers prepared by the DRA should be objective rather than subjective, and reasons should be given for all recommendations. At least the following information should appear in papers presented to the expert advisory body.

- The company's letter of application.
- The evaluator's summary of the data set and his/her recommendations, with reasons. Include or attach at least:
    - Copies of the specifications of the API and the finished product, with notes as to any aspects the evaluator finds unacceptable;
    - A summary of stability data, the applicant's recommended shelf-life and the evaluator's recommended shelf-life;
    - A summary and evaluation of the evidence as to interchangeability; the evaluator should state what calculations, if any, he or she has duplicated during the evaluation;
    - A copy of the proposed product information with the evaluator's comments and recommendations.

- Details of sites of manufacture and certification of GMP. The evaluator should state whether he or she believes these to be satisfactory.
- The results of any quality control laboratory testing of the product and any inspection of local manufacturing activities, such as packaging.

18. Variations

As a matter of principle, applications to vary an existing marketing authorization should not be discouraged because they are often intended to improve quality (such as stability, batch-to-batch consistency, and analytical methodology) or product information (for example, updates to information on adverse reactions). Prior advice of such changes is to be encouraged; variations should therefore be processed as quickly as possible. A balance must be maintained between not placing the company at a disadvantage for making the application and nevertheless ensuring that the change has been adequately validated.

Variations that are submitted for approval should not automatically trigger a request for a full data set or a full evaluation. Data requirements, and the evaluation, should be limited to those needed to validate the variation. Changes that require a new marketing authorization number may not necessarily need to be supported by a full data set. For example, a change of or additional trade name and/or market authorization holder may require a new marketing authorization number, but would not require data provided that the new authorization holder certifies that (a) the product is identical in every respect to the produce that is currently authorized and (b) the holder of the old marketing authorization agrees to the change.

19. Periodic reviews of marketing authorizations

The intention of a periodic review is to consolidate the information held by the DRA.

Any pharmaceutical (manufacturing, quality control, shelf-life, container labelling, etc.) variations/changes made to the product since the first marketing authorization or the last periodic review should have been either changes for which prior approval has been obtained or those not requiring prior approval. Any safety updates should have been made when the relevant safety information became sufficiently well established as defined by CIOMS (*24*, p.39). GMP practices should have been maintained and, as necessary, improved at all sites of manufacture.

The following information should be submitted with each periodic review.

1. Updated WHO-type certificates for each foreign site of manufacture of the finished product (see Annex 2, section 3.5). *When the proposed WHO guidelines for certification of APIs have been finalized, it may also be necessary to supply WHO-type API certificates for sites of manufacture of APIs.*
2. Updated certificates of GMP for domestic manufacturing sites.
3. A chronological list of all:
   (a) Approved pharmaceutical variations of any type, and all amendments made to product information since the first marketing authorization or the last periodic review. The dates of approval and file reference for each change should be provided; and
   (b) A set of current specifications for the API(s) and finished product, including test methods in sufficient detail for them to be replicated by another laboratory.

The periodic review should not be used as an opportunity to seek authorization for new variations. These should be subject to separate application. Nor should it be a means of regularizing unauthorized changes to pharmaceutical information or to product information.

Annex 8: Ethical criteria for medicinal drug promotion[1]

Contents

[1] World Health Organization, Geneva, 1988

Resolution WHA41.17 adopted by the Forty-first World Health Assembly, 13 May 1988

Ethical criteria for medicinal drug promotion

The Forty-first World Health Assembly,

Recalling resolutions WHA21.41 and WHA39 77;

Having considered the report of the Executive Board concerning the ethical criteria for medicinal drug promotion based on a draft prepared by an international group of experts;

Convinced that observance of ethical criteria for medicinal drug promotion by all parties concerned will contribute to a more rational use of drugs;

1. THANKS the international group of experts for its work;

2. ENDORSES the ethical criteria for medicinal drug promotion that are annexed to this resolution, on the understanding that they constitute general principles that could be adapted by governments to countries' circumstances as appropriate to their political, economic, cultural, social, educational, scientific and technical situation, their national laws and regulations, disease profile, therapeutic traditions, and the level of development of their health system, and that they do not constitute legal obligations;

3. URGES Member States:

   (1) to take account of these ethical criteria in developing their own appropriate measures to ensure that medicinal drug promotion supports the aim of improving health care through the rational use of drugs;

   (2) to monitor and enforce, where appropriate, the implementation of the measures they have developed;

4. APPEALS to pharmaceutical manufacturers and distributors, the promotion industry, health personnel involved in the prescription, dispensing, supply and distribution of drugs, universities and other teaching institutions, professional associations, patient and consumer groups, the professional and general media (including publishers and editors of medical journals and related publications), and the public:

   (1) to use these criteria as appropriate to their spheres of competence, activity and responsibility;

   (2) to adopt measures based on these criteria as appropriate, and monitor and enforce their standards;

5. REQUESTS the Director-General

   (1) to ensure the wide dissemination of these criteria in all official languages;

   (2) to follow the practice of these criteria and to report to the Executive Board from time to time as appropriate.

Ethical Criteria

Introduction

1. Following the WHO Conference of Experts on the Rational Use of Drugs held in Nairobi in November 1985, WHO prepared a revised drug strategy which was endorsed by the Thirty-ninth World Health Assembly in May 1986 in resolution WHA39.27. This strategy includes, among other components, the establishment of ethical criteria for drug promotion based on the updating and extension of the ethical and scientific criteria established in 1968 by the Twenty-first World Health Assembly in resolution WHA21.41. The criteria that follow have been prepared in compliance with the above on the basis of a draft elaborated by an international group of experts.

Objective

2. The main objective of ethical criteria for medicinal drug promotion is to support and encourage the improvement of health care through the rational use of medicinal drugs.

Ethical criteria

3. The interpretation of what is ethical varies in different parts of the world and in different societies. The issue in all societies is what is proper behaviour. Ethical criteria for drug promotion should lay the foundation for proper behaviour concerning the promotion of medicinal drugs, consistent with the search for truthfulness and righteousness. The criteria should thus assist in judging if promotional practices related to medicinal drugs are in keeping with acceptable ethical standards.

Applicability and implementation of criteria

4. These criteria constitute general principles for ethical standards which could be adapted by governments to national circumstances as appropriate to their political, economic, cultural, social, educational, scientific and technical situation, laws and regulations, disease profile, therapeutic traditions and the level of development of their health system. They apply to prescription and non-prescription medicinal drugs ("over-the-counter drugs"). They also apply generally to traditional medicines as appropriate, and to any other product promoted as a medicine. The criteria could be used by people in all walks of life; by governments; the pharmaceutical industry (manufacturers and distributors); the promotion industry (advertising agencies, market research organizations and the like); health personnel involved in the prescription, dispensing, supply and distribution of drugs; universities and other teaching institutions; professional associations; patients' and consumer groups; and the professional and general media (including; publishers and editors of medical journals and related publications). All these are encouraged to use the criteria as appropriate to their spheres of competence, activity and responsibility. They are also encouraged to take the criteria into account in developing their own sets of ethical standards in their own field relating to medicinal drug promotion.

5. The criteria do not constitute legal obligations; governments may adopt legislation or other measures based on them as they deem fit. Similarly, other groups may adopt self-regulatory measures based on them. All these bodies should monitor and enforce their standards.

Promotion

6. In this context, "promotion" refers to all informational and persuasive activities by manufactures and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs.

7. Active promotion within a country should take place only with respect to drugs legally available in the country. Promotion should be in keeping with national health policies and in compliance with national regulations, as well as with voluntary standards where they exist. All promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks. The word "safe" should only be used if properly qualified. Comparison of products should be factual, fair and capable of substantiation. Promotional material should not be designed so as to disguise its real nature.

8. Scientific data in the public domain should be made available to prescriber and any other person entitled to receive it, on request, as appropriate to their requirements. Promotion in the form of financial or material benefits should not be offered to or sought by health care practitioners to influence them in the prescription of drugs.

9. Scientific and educational activities should not be deliberately used for promotional purposes.

Advertising

(a) Advertisements in all forms to physicians and health-related professionals

10. The wording and illustrations in advertisements to physicians and related health professionals should be fully consistent with the approved scientific data sheet for the drug concerned or other source of information with similar content. The text should be fully legible.

11. Some countries require that advertisements should contain full product information, as defined by the approved scientific data sheet or similar document, for a given period from the date of first promotion or for the full product life. Advertisements that make a promotional claim should at least contain summary scientific information.

12. The following list, based on the sample drug information sheet contained in the second report of the WHO Expert Committee on the Use of Essential Drugs[1] and appended for ease of reference, can serve as an illustration of the type of information that such advents should usually contain, among others:

- the name(s) of the active ingredient(s) using either international nonproprietary names (INN) or the approved generic name of the drug;
- the brand name;
- content of active ingredients) per dosage form or regimen;
- name of other ingredients known to cause problems;
- approved therapeutic uses;

[1] WHO Technical Report Series, No. 722, 1985, p.43

- dosage form or regimen;
- side-effects and major adverse drug reactions;
- precautions, contra-indications and warnings;
- major interactions;
- name and address of manufacturer or distributor;
- reference to scientific literature as appropriate.

13. Where advertisements are permitted without claims (reminder advertisements), they ought to include at least the brand name, the international nonproprietary name or approved generic name, the name of each active ingredient, and the name and address of the manufacturer or distributor for the purpose of receiving further information.

(b) Advertisements in all forms to the general public

14. Advertisements to the general public should help people to make rational decisions on the use of drugs determined to be legally available without a prescription. While they should take account of peoples legitimate desire for information regarding their health, they should not take undue advantage of people's concern for their health. They should not generally be permitted for prescription drugs or to promote drugs for certain serious conditions that can be treated only by qualified health practitioners, for which certain countries have established lists. To fight drug addiction and dependency, scheduled narcotic and psychotropic drugs should not be advertised to the general public. While health education aimed at children is highly desirable, drug advertisements should not be directed at children. Advertisements may claim that a drug can cure, prevent, or relieve an ailment only if this can be substantiated. They should also indicate, where applicable, appropriate limitations to the use of the drug.

15. When lay language is used, the information should be consistent with the approved scientific data sheet or other legally determined scientific basis for approval. Language which brings about fear or distress should not be used.

16. The following list serves as an illustration of the type of information advertisements to the general public should contain, taking into account the media employed:

- the name(s) of the active ingredient(s) using either international nonproprietary names (INN) or the approved generic name of the drug;
- the brand name;
- major indication(s) for use;
- major precautions, contra-indications and warnings;
- name and address of manufacturer or distributor.

Information on price to the consumer should be accurately and honestly portrayed.

Medical representatives

17. Medical representatives should have an appropriate educational background. They should be adequately trained. They should possess sufficient medical and technical knowledge and integrity to present information on products and carry out other promotional activities in an accurate and responsible manner. Employers are responsible for the basic and continuing training of their representatives. Such training should include instruction regarding appropriate ethical conduct taking into consideration the WHO criteria. In this context, exposure of medical representatives

and trainees to feedback from the medical and allied professions and from independent members of the public, particularly regarding risks, can be salutary.

18. Medical representatives should make available to prescribers and dispensers complete and unbiased information for each product discussed, such as an approved scientific data sheet or other source of information with similar content.

19. Employers should be responsible for the statements and activities of their medical representatives. Medical representatives should not offer inducements to prescribers and dispensers. Prescribers and dispensers should not solicit such inducements. In order to avoid over promotion, the main part of the remuneration of medical representatives should not be directly related to the volume of sales they generate.

Free samples of prescription drugs for promotional purposes

20. Free samples of legally available prescription drugs may be provided in modest quantities to prescribers, generally on request.

Free samples of non-prescription drugs to the general pubic for promotional purposes

21. Countries vary in their practices regarding the provision of free samples of non-prescription drugs to the general public, some countries permitting it, some not. Also, a distinction has to be made between provision of free drugs by health agencies for the care of certain groups and the provision of free samples to the general public for promotional purposes. The provision of free samples of non-prescription drugs to the general public for promotional purposes is difficult to justify from a health perspective. If this practice is legally permitted in any country, it should be handled with great restraint.

Symposia and other scientific meetings

22. Symposia are useful for disseminating information The objective scientific content of such meetings should be paramount, and presentations by independent scientists and health professionals are helpful to this end. Their educational value may be enhanced if they are organized by scientific or professional bodies.

23. The fact of sponsorship by a pharmaceutical manufacturer or distributor should be clearly stated in advance, at the meeting and in any proceedings. The latter should accurately reflect the presentations and discussions. Entertainment or other hospitality, and any gifts offered to members of the medical and allied professions, should be secondary to the main purpose of the meeting and should be kept to a modest level.

24. Any support to individual health practitioners to participate in any domestic or international symposia should not be conditional upon any obligation to promote any medicinal product.

Post-marketing scientific studies, surveillance and dissemination of information

25. Post-marketing clinical trials for approved medicinal drugs are important to ensure their rational use. It is recommended that appropriate national health authorities be made aware of any such studies and that relevant scientific and ethical committees confirm the validity of the research. Intercountry and regional cooperation in such studies may be useful. Substantiated information on

such studies should be reported to the appropriate national health authorities and disseminated as soon as possible.

26. Post-marketing scientific studies and surveillance should not be misused as a disguised form of promotion.

27. Substantiated information on hazards associated with medicinal drugs should be reported to the appropriate national health authority as a priority, and should be disseminated internationally as soon as possible.

Packaging and labelling

28. Appropriate information being important to ensure the rational use of drugs, all packaging and labelling material should provide information consistent with that approved by the country's drug regulatory authority. Where one does not exist or is rudimentary, such material should provide information consistent with that approved by the drug regulatory authority of the country from which the drug is imported or other reliable sources of information with similar content. Any wording and illustration on the package and label should conform to the principles of ethical criteria enunciated in this document.

Information for patients: package inserts, leaflets and booklets

29. Adequate information on the use of medicinal drugs should be made available to patients. Such information should be provided by physicians or pharmacists whenever possible. When package inserts or leaflets are required by governments, manufacturers or distributors should ensure that they reflect only the information that has been approved by the country’s drug regulatory authority. If package inserts or leaflets are used for promotional purposes, they should comply with the ethical criteria enunciated in this document. The wording of the package inserts or leaflets, if prepared specifically for patients, should be in lay language on condition that the medical and scientific content is properly reflected.

30. In addition to approved package inserts and leaflets wherever available, the preparation and distribution of booklets and other informational material for patients and consumers should be encouraged as appropriate. Such material should also comply with the ethical criteria enunciated in this document.

Promotion of exported drugs

31. Ethical criteria for the promotion of exported drugs should be identical with those relating to drugs for domestic use. It is desirable that exporting and importing countries that have not already done so should use the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

|Appendix

Sample Drug Information Sheet[2]

Drug information sheets

Various types of information are needed by prescriber and consumers to ensure the safe and effective use of drugs. The following list is a sample that should be adjusted to meet the needs and abilities of the prescriber.

(1) International Nonproprietary Name (INN) of each active substance.

(2) Pharmacological data:. a brief description of pharmacological effects and mechanism of action.

(3) Clinical information:

(a) Indications: whenever appropriate, simple diagnostic criteria should be provided.
(b) Dosage regimen and relevant pharmacokinetic data:
- average and range for adults and children;
- dosing interval;
- average duration of treatment;
- special situations, e.g., renal, hepatic, cardiac, or nutritional insufficiencies that require either increased or reduced dosage.

(c) Contra-indications.
(d) Precautions and warnings (reference to pregnancy, lactation, etc.).
(e) Adverse effects (quantify by category, if possible).
(f) Drug interactions (include only if clinically relevant; drugs used for self-medication should be included).
(g) Overdosage:
- brief clinical description of symptoms;
- non-drug treatment and supportive therapy;
- specific antidotes.

(4) Pharmaceutical information:

(a) Dosage forms.
(b) Strength of dosage form.
(c) Excipients.
(d) Storage conditions and shelf-life (expiry date).
(e) Pack sizes.
(f) Description of the product and package.
(g) Legal category (narcotic or other controlled drug, prescription or non-prescription).
(h) Name and address of manufacturer(s) and importer(s).

[2] Reproduced from *The use of essential drugs: second report of the WHO Expert Committee on the Use of Essential Drugs* (WHO Technical Report Series, No. 722,1985, p. 43.

Annex 9: Model marketing authorization letter

The Managing Director
[Name of company]
[Address]
[Date]:

Attention: Regulatory Affairs Manager

Dear Sir/Madam

I refer to the application dated *[date of application]* for marketing authorization of:

Proprietary name (trade name)
Approved generic name(s)
Strength(s) per dosage unit
Dosage form
Name of authorization holder*
*[*Must be a person or company in the country in which marketing is being authorized. This letter should normally be addressed to the marketing authorization holder.]*

Evaluation of the application has been completed. Approval under *[name of legislation]* is granted, subject to the conditions in this letter and its attachments. This letter and its attachments constitute the marketing authorization. The details of this marketing authorization are as follows.

Marketing authorization number
Date from which marketing is authorized
Expiry date of this marketing authorizations

The conditions which apply are as follows..

General conditions applying to all products

- The product(s) must conform with all the details provided in your application and as modified in subsequent correspondence.
- No changes may be made to the product without prior approval, except for changes of the type listed in *[name of regulatory authority]*'s policy on "Changes to pharmaceutical aspects which may be made without prior approval". Conditions in that policy apply.
- The approved sites of manufacture are those in Attachment 1.
- The approved shelf-life is that in Attachment 2.
- The only Product Information (PI) that may be supplied with or for this product must be the PI that is approved. Attachment 3 is a copy of the approved PI.
- The Product information may not be altered without prior approval, except for safety updates that further restrict use of the product. Any such safety-related changes must be notified to *[name of regulatory authority]* within five days of making the change.

- The product information must include the marketing authorization number and the date from which marketing is authorized. This information must appear in the top right hand corner of the first page of the Product information, in letters of at least 1.5 mm tall.
- All advertising and promotion of the product(s) must be consistent with the agreed product information.

- *Additional specific conditions applying to this product*:
- [...for example, “Distribution is restricted to hospitals specializing in oncology”.....]
- [.....]
- [.....]

If you have any doubt as to the meaning of this letter and its attachments, you should contact the undersigned prior to marketing the product.

Yours faithfully

[Name]
[Signature]

AUTHORIZED PERSON UNDER *[name of legislation]*

MARKETING AUTHORIZATION
Attachment 1

Product

Proprietary name (trade name)
Approved generic name(s)
Strength(s) per dosage unit
Dosage form
Name of authorization holder
Marketing authorization number
Date from which marketing is authorized
Expiry date of this marketing authorization

The approved manufacturers are as follows.

Production stage	Name of site	Street address of site	Manufacturing step
[Active pharmaceutical ingredient I]			Production
[Active pharmaceutical ingredient II]			Production
Finished product			[For example granulation]
			[For example sterilization]
			[For example packaging]
			[For example quality control]

MARKETING AUTHORIZATION
Attachment 2

Product

Proprietary name (trade name)
Approved generic name(s)
Strength(s) per dosage unit
Dosage form
Name of authorization holder
Marketing authorization number
Date from which marketing is authorized
Expiry date of this authorization

Shelf-life

The approved shelf -life of this product when packaged and labelled as detailed in the application and modified in subsequent correspondence is as follows.

Pack	Shelf-life	Storage conditions
[For example, PVC/Al blisters, 25 and 50 tablets per blister]	18 months	Store below 30°C Protect from moisture
[For example, HDPE bottles]	3 years	Store below 30°C Protect from moisture

Restrictions on sale or distribution

[Normally one of these, and possibly different restrictions for different strengths.

- Scheduled narcotic;
- Restricted prescription-only distribution (specify - for example, hospitals only);
- Prescription only;
- Pharmacy only;
- Over the counter (OTC)].

Annex 10: Model List of Variations (Changes) to Pharmaceutical Aspects of Registered Products which may be made without Prior Approval

Annexes, glossary, abbreviations and references are as those in the main text.

Subject to the general and specific conditions that follow, applicants may make certain changes to pharmaceutical aspects of products without prior approval from the DRA.

*The following **general conditions** apply to all changes made without prior approval:*

(a) The change should be listed below as one that may be made without prior approval.
(b) It must have been demonstrated (validated) that the change does not reduce the quality, safety or efficacy of the product, and that the pharmaceutical properties of the product -e.g. particle size of the API, dissolution rate of solid dosage forms - have not been altered. It is the responsibility of the marketing authorization holder to ensure that all necessary validation has been conducted. The validation requirements listed below under "additional conditions" are the minimum.
(c) If the DRA requests a copy of the validation data, they must be supplied within one month of the request.
(d) The DRA must be notified of the change if the list below indicates that notification is required. A date of implementation must be included in the notification. Notifications must be made either in advance of the change or not later than one month after implementation.

Changes that may be made without prior approval are listed below. ***Specific conditions*** apply in some cases as indicated. No other changes may be made without prior approval.

1. Analytical methodology for the finished product. On condition that (a) validation shows that the new method is equivalent to or better than the existing method, and (b) major changes (e.g. ultra violet assay to high-pressure liquid chromatography (HPLC)) are notified.
2. Additional tests and limits for starting materials or finished products. On condition that these do not reflect a change in processing, e.g. from a fine to microfine particle size.
3. Alteration of methods of manufacture and manufacturing equipment. On condition that (a) the product is not a slow or otherwise modified release product, and (b) a new stability study has been commenced on at least two batches of the altered product.
4. A change in the content of an excipient of up to ±5%.
5. Changes to flavours, perfumes or colours. On condition that (a) any new colours are permitted by the European Union's "List of permitted food colours" (*19*) or FDA's "Inactive ingredient guide" (*21*), (b) the change is notified, (c) stability data are available on two batches of the altered product for at least three months under accelerated conditions (as defined in Annex 11) or one year under non-accelerated conditions, and (d) a new stability study has been commenced on at least two batches of the altered product for the full duration of the shelf-life.
6. Alteration of the quantitative composition of a tablet or capsule coating amounting to less than 2% of the total weight of the tablet or capsule. On condition that (a) the coating has no modified-release properties, (b) there is no API in the coating, (c) any new colours are permitted by the European Union's "List of permitted food colours (*19*) or by FDA's "Inactive ingredient guide" (*21*), and (d) the change is notified.
7. Changes to the volume of granulating fluid of up to ±15%.
8. Changes in batch size. On condition that a stability study has been commenced on at least one full scale production batch.
9. Changes to the quantitative content of agents whose only function is to make the product viscous. On condition that (a) it has been demonstrated that any solid material present is at least equally well suspended, and (b) a stability study has been commenced on at least two batches of the altered product.

10. Changes to the container/closure system in immediate contact with the product, or additional types of container/closure. On condition that (a) the product is not a sterile product, (b) the new system offers equal or better protection to the product, (c) stability data are available on two batches of the product in the new container for at least three months under accelerated conditions (as defined in Annex 11) or one year under non-accelerated conditions, (d) a stability study has been commenced on at least two batches of the altered product for the full duration of the shelf-life, and (e) the change is notified. Changes may not be made to labelling without prior approval.
11. Changes to parts of the container not in contact with the product, but not including labelling - see 12 below.
12. Changes may not be made to labelling without prior approval, except for changes to layout without alteration of text or meaning. Pictures or diagrams may not be added without prior approval because they may imply an unapproved indication.
13. Changes in imprints or marks on solid dosage forms. On condition that (a) these do not imply an unapproved indication or patient population, (b) no unapproved colour (as defined above) is introduced, (c) any changes to scoring are consistent with the dose schedules in the approved product information, and (d) the change is notified
14. *[In some countries, depending on legislation.]* Change to the marketing authorization holder (name, address and/or legal entity). On condition that there is no change to the product, including sites of manufacture.

New sites of manufacture require prior approval, because the DRA should see evidence of compliance with GMP, e.g. a WHO-type certificate (see Annex 2). Changes or additions to pack size also require prior approval, because the new size must be consistent with the approved uses of the product.

Notifications of variations, and applications to vary, should be accompanied by the statement

> No variations have been made other than (1) those notified herewith and (2) changes which are permitted without notification or prior approval according to the guidelines of the drug regulatory authority of .....

Annex 11 *Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms[1]

General

The stability of finished pharmaceutical products depends, on the one hand, on environmental factors such as ambient temperature, humidity and light, and, on the other, on product-related factors, e.g. the chemical and physical properties of the active substance and of pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system and the properties of the packaging materials.

For established drug substances in conventional dosage forms, literature data on the decomposition process and degradability of the active substance (*1*) are generally available together with adequate analytical methods. Thus, the stability studies may be restricted to the dosage forms.

Since the actual stability of a dosage form will depend to a large extent on the formulation and packaging-closure system selected by the manufacturer, stability considerations, e.g. selection of

[1] Also published as Annex 5 of WHO Technical Report Series, No. 863, 1996

excipients, determination of their level and process development, should be given high priority

in the developmental stage of the product. The possible interaction of the drug product with the packaging material in which it will be delivered, transported and stored throughout its shelf-life must also be investigated.

The shelf-life should be established with due regard to the climatic zone(s) (see section 2) in which the product is to be marketed. For certain preparations, the shelf-life can be guaranteed only if specific storage instructions are complied with.

The storage conditions recommended by manufacturers on the basis of stability studies should guarantee the maintenance of quality, safety, and efficacy throughout the shelf-life of a product. The effect on products of the extremely adverse climatic conditions existing in certain countries to which they may be exported calls for special consideration (see section 6).

To ensure both patient safety and the rational management of drug supplies, it is important that the expiry date and, when necessary, the storage conditions are indicated on the label.

Definitions

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

accelerated stability testing
Studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from real-time stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

batch
A defined quantity of product processed in a single process or series of processes and therefore expected to be homogeneous. In continuous manufacture, the batch must correspond to a defined fraction of production, characterized by its intended homogeneity.

climatic zones
The four zones into which the world is divided based on the prevailing annual climatic conditions (see section 2).

expiry date
The date given on the individual container (usually on the label) of a drug product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life period to the date of manufacture.

mean kinetic temperature
The single test temperature for a drug product corresponding to the effects on chemical reaction kinetics of a given temperature-time distribution. A mean kinetic temperature is calculated for each of the four world climatic zones according to the formula developed by Haynes (*2*). It is normally higher

than the arithmetic mean temperature.

real-time (long-term) stability studies
Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf-life, to confirm the projected shelf-life, and to recommend storage conditions.

shelf-life
The period of time during which a drug product, if stored correctly, is expected to comply with the specification[1] as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

stability
The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf-life.

stability tests
A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage conditions.

supporting stability data
Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers other than those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf-life and storage conditions.

utilization period ,
The period of time during which a reconstituted preparation or the finished dosage form in an opened multidose container can be used.

1. **Stability testing**

The main objectives and uses of stability testing are shown in Table 1.

1.1 ***In the development phase***

Accelerated stability tests provide a means of comparing alternative formulations, packaging materials, and/or manufacturing processes in short-term experiments. As soon as the final formulation and manufacturing process have been established, the manufacturer carries out a series of accelerated stability tests which will enable the stability of the drug product to be predicted and its shelf-life and storage conditions determined. Real-time studies must be started at the same time for confirmation purposes. Suitable measures should be taken to establish the utilization period for preparations in multidose containers, especially for topical use.

[1] Shelf-life specification means the requirements to be met throughout the shelf-life of the drug product (should not be confused with "release specifications).

1.2 *For the registration dossier*

The drug regulatory authority will require the manufacturer to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. The data submitted are obtained from both accelerated and real-time studies. Published and/or recently obtained experimental supporting stability data may also be submitted, e.g. on the stability of active ingredients and related formulations.

Table 1 **Main objectives of stability testing**

Objective	Type of study	Use
To select adequate (from the viewpoint stability) formulations and container-closure systems	Accelerated	Development of the of product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control

Where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection or a concentrate for oral suspension), "in use" stability data must be submitted to support the recommended storage time and conditions for those dosage forms.

With the approval of the drug regulatory authority, a tentative (provisional) shelf-life is often established, provided that the manufacturer has undertaken, by virtue of a signed statement, to continue and complete the required studies and to submit the results to the registration authority.

1.3 *In the post-registration period*

The manufacturer must carry out on-going real-time stability studies to substantiate the expiry date and the storage conditions previously projected. The data needed to confirm a tentative shelf-life must be submitted to the registration body. Other results of on-going stability studies are verified in the course of GMP inspections. To ensure the quality and safety of products with particular reference to degradation, national health authorities should monitor the stability and quality of preparations on the market by means of a follow-up inspection and testing programme.

Once the product has been registered, additional stability studies are required whenever major modifications are made to the formulation, manufacturing process, packaging or method of preparation. The results of these studies must be communicated to the competent drug regulatory authorities.

2. **Intended market**

The design of the stability testing programme should take into account the intended market and the climatic conditions in the area in which the drug products will be used.

Four climatic zones can be distinguished for the purpose of worldwide stability testing, as follows:

- Zone I: temperate.
- Zone II: subtropical, with possible high humidity.
- Zone III: hot/dry.
- Zone IV: hot/humid.

(See Schumacher P. Aktuelle Fragen zur Haltbarkeit von Arzneimitteln. [Current questions on drug stability.] *Pharmazeutische Zeitung*, 1974, 1 19:321-324.)

The mean climatic conditions, calculated data and derived storage conditions in these zones are summarized in Tables 2 and 3.

Since there are only a few countries in zone I, the manufacturer would be well advised to base stability testing on the conditions in climatic zone II when it is intended to market products in temperate climates. For countries where certain regions are situated in zones III or IV, and also with a view to the global market, it is recommended that stability testing programmes should be based on the conditions corresponding to climatic zone IV.

In a stability study, the effect on the product in question of variations in temperature, time, humidity, light intensity and partial vapour pressure are investigated. The effective or mean kinetic temperature therefore reflects the actual situation better than the measured mean temperature; a product kept for I month at 20 °C and I month at 40 °C will differ from one kept for 2 months at 30 °C. Moreover, the storage conditions are often such that the temperature is higher than the average meteorological data for a country would indicate.

Table 2
Mean climatic conditions: measured data in the open air and in the storage room[1]

Climatic zone	Measured data in the open air		Measured data in the storage room	
	°C%	RH	°C	RH
I	10.9	75	18.7	45
II	17.0	70	21.1	52

III	24.4	39	26.0	54
IV	26.5	77	28.4	70

[1] RH = relative humidity.

Table 3
Mean climatic conditions: calculated data and derived storage conditions[1]

Climatic zone	Calculated data			Derived storage conditions (for real-time studies)	
	°C[2]	°C MKT[3]	% RH[4]	°C	% RH
I	20.0	20.0	42	21	45
II	21.6	22.0	52	25	60
III	26.4	27.9	35	30	35
IV	26.7	27.4	76	30	70

[1] Based on: Grimm W. Storage conditions for stability testing in the EC, Japan and USA; the most important market for drug products. *DN9 development and industrial pharmacy,* 1993, 19:2795-2830.

[2] Calculated temperatures are derived from measured temperatures, but all measured temperatures of less than 19 °C were set equal to 19 °C.

[3] MKT = mean kinetic temperature (see p.198).

[4] RH = relative humidity.

For some dosage forms, especially liquid and semi-solid ones, the study design may also need to include subzero temperatures, e.g. –10 to –20 °C (freezer), freeze-thaw cycles or temperatures in the range 2–8 °C (refrigerator). For certain preparations it may be important to observe the effects caused by exposure to light.

3. Design of stability studies

Stability studies on a finished pharmaceutical product should be designed in the light of the properties and stability characteristics of the drug substance as well as the climatic conditions of the intended market zone. Before stability studies of dosage forms are initiated, information on the stability of the drug substance should be sought, collected and analysed. Published information on stability is available on many well established drug substances.

3.1 *Test samples*

For registration purposes, test samples of products containing fairly stable active ingredients are taken from two different production batches; in contrast, samples should be taken from three batches of products containing easily degradable active ingredients or substances on which limited stability data are available. The batches to be sampled should be representative of the manufacturing process, whether pilot plant or full production scale. Where possible, the batches to be tested should be manufactured from different batches of active ingredients.

In on-going studies, current production batches should be sampled in accordance with a predetermined schedule. The following sampling schedule is suggested:

- one batch every other year for formulations considered to be stable, otherwise one batch per year;
- one batch every 3-5 years for formulations for which the stability profile has been established, unless a major change has been made, e.g. in the formulation or the method of manufacture.

Detailed information on the batches should be included in the test records, namely the packaging of the drug product, the batch number, the date of manufacture, the batch size, etc.

3.2 *Test conditions*

3.2.1 *Accelerated studies*

An example of conditions for the accelerated stability testing of products containing relatively stable active ingredients is shown in Table 4.

For products containing less stable drug substances, and those for which limited stability data are available, it is recommended that the duration of the accelerated studies for zone II should be increased to 6 months.

Table 4
Example of conditions for accelerated stability testing of products containing relatively stable active ingredients

Storage temperature (°C)	Relative humidity (%)	Duration of studies (months)
	Zone IV- For hot climatic zones or global market:	
40 ± 2	75 ± 5	6
	Zone 11- For temperate and subtropical climatic zones:	
40 ± 2	75 ± 5	3

Alternative storage conditions may be observed, in particular, storage for 6 months at a temperature of at least I5 °C above the expected actual storage temperature (together with the appropriate relative humidity conditions). Storage at higher temperatures may also be recommended, e.g. 3 months at 45-

50 °C and 75% relative humidity (RH) for zone IV.

Where significant changes (see below) occur in the course of accelerated studies, additional tests at intermediate conditions should be conducted, e.g. 30 ± 2 °C and 60 ± 5% RH. The initial registration application should then include a minimum of 6 months' data from a 1-year study.

A significant change is considered to have occurred if:

- the assay value shows a 5% decrease as compared with the initial assay value of a batch;
- any specified degradation product is present in amounts greater than its specification limit;
- the pH limits for the product are no longer met;
- the specification limits for the dissolution of 12 capsules or tablets are no longer met;
- the specifications for appearance and physical properties, e.g. colour, phase separation, caking, hardness, are no longer met.

Storage under test conditions of high relative humidity is particularly important for solid dosage forms in semi-permeable packaging. For products in primary containers designed to provide a barrier to water vapour, storage conditions of high relative humidity are not necessary. As a rule, accelerated studies are less suitable for semi-solid and heterogeneous formulations, e.g. emulsions.

3.2.2 *Real-time studies*

The experimental storage conditions should be as close to the projected actual storage conditions in the distribution system as practicable (see Table 3). For registration purposes, the results of studies of at least 6 months' duration should be available at the time of registration. However, it should be possible to submit the registration dossier before the end of this 6-month period. Real-time studies should be continued until the end of the shelf-life.

3.3 Frequency of testing and evaluation of test results

In the development phase and for studies in support of an application for registration, a reasonable frequency of testing of products containing relatively stable active ingredients is considered to be:

- for accelerated studies, at 0, 1, 2, 3 and, when appropriate, 6 months;
- for real-time studies, at 0, 6 and 12 months, and then once a year.

For on-going studies, samples may be tested at 6-month intervals for the confirmation of the provisional shelf-life, or every 12 months for well established products. Highly stable formulations may be tested after the first 12 months and then at the end of the shelf-life. Products containing less stable drug substances and those for which stability data are available should be tested every 3 months in the first year, every 6 months in the second year, and then annually.

Test results are considered to be positive when neither significant degradation nor changes in the physical, chemical and, if relevant, biological and microbiological properties of the product have been observed, and the product remains within its specification.

4. Analytical methods

A systematic approach should be adopted to the presentation and evaluation of stability information, which should include, as necessary, physical, chemical, biological and microbiological test

characteristics.

All product characteristics likely to be affected by storage, e.g. assay value or potency, content of products of decomposition, physicochemical properties (hardness, disintegration, particulate matter, etc.), should be determined; for solid or semi-solid oral dosage forms, dissolution tests should be carried out.

Test methods to demonstrate the efficacy of additives, such as antimicrobial agents, should be used to determine whether such additives remain effective and unchanged throughout the projected shelf-life.

Analytical methods should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. The assay methods chosen should be those indicative of stability. The tests for related compounds or products of decomposition should be validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity.

A checklist similar to that used in the WHO survey on the stability of pharmaceutical preparations included in the WHO Model List of Essential Drugs (Appendix 1) can be used to determine the other stability characteristics of the product.

5. Stability report

A stability report must be established for internal use, registration purposes, etc., giving details of the design of the study, as well as the results and conclusions.

The results should be presented as both a table and a graph. For each batch, the results of testing both at the time of manufacture and at different times during storage should be given. A standard form should be prepared in which the results for each pharmaceutical preparation can be summarized (see Appendix 2).

The stability of a given product, and therefore the proposed shelf-life and storage conditions, must be determined on the basis of these results.

6. Shelf-life and recommended storage conditions

Shelf-life is always determined in relation to storage conditions. If batches of a product have different stability profiles, the shelf-life proposed should be based on the stability of the least stable, unless there are justifiable reasons for doing otherwise.

The results of stability studies, covering the physical, chemical, biological, microbiological and biopharmaceutical quality characteristics of the dosage form, as necessary, are evaluated with the objective of establishing a tentative shelf-life. Statistical methods are often used for the interpretation of these results. Some extrapolation of real-time data beyond the observed range, when accelerated studies support this, is acceptable.

A tentative shelf-life of 24 months may be established provided the following conditions are satisfied:

- the active ingredient is known to be stable (not easily degradable);
- stability studies as outlined in section 3.2 have been performed and no significant changes have been observed;

- supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more;
- the manufacturer will continue to conduct real-time studies until the proposed shelf-life has been covered, and the results obtained will be submitted to the registration authority.

Products containing less stable active ingredients and formulations not suitable for experimental studies on storage at elevated temperature (e.g. suppositories) will need more extensive real-time stability studies. The proposed shelf-life should then not exceed twice the period covered by the real-time studies.

After the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:

- store under normal storage conditions;[2]
- store between 2 and 8 °C (under refrigeration, no freezing);
- store below 8 °C (under refrigeration);
- store between -5 and –0 °C (in a freezer);
- store below –18 °C (in a deep freezer).

Normal storage conditions have been defined by WHO (*3*) as: “storage in dry, well-ventilated premises at temperatures of 15-25 °C or, depending on climatic conditions, up to 30 °C. Extraneous odours, contamination, and intense light have to be excluded."

These conditions may not always be met, bearing in mind the actual situation in certain countries. "Normal conditions" may then be defined at the national level. Recommended storage conditions must be determined in the light of the conditions prevailing within the country of designated use.

General precautionary statements, such as "protect from light" and/or "store in a dry place", may be included, but should not be used to conceal stability problems.

If applicable, recommendations should also be made as to the utilization period and storage conditions after opening and dilution or reconstitution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

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[2] This statement may not always be required for products intended for areas with a temperate climate.

Official, international and national guidelines

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Appendix 1
Survey on the stability of pharmaceutical preparations included in the WHO Model List of Essential Drugs: answer sheet

A checklist similar to that shown here can be used to determine the stability characteristics of a product.

Name of reporting person Address Country
Climatic zone

NAME OF ESSENTIAL DRUG:

Description of product

Dosage form

1. tablet	coated	uncoated
2. capsule	hard	soft
3. injection	liquid	powder
4. oral liquid	solution	suspension
5. topical semi-solid	cream	ointment
6. eye preparations	liquid	semi-solid
7. other (please state)		

Packaging (material and type)

1. glass	bottle	vial	ampoule
2. plastic	bottle	vial	ampoule
3. paper	bag	bag	
4. metal			
5. blister pack			
6. other (please state)			

State of packaging intact damaged

Storage conditions
according to the manufacturer's indications? yes no

Shelf-life (if available)
claimed by the manufacturer .....years .....months
percentage elapsed when tested ..... %

Source of product tested

1. manufactured in country of use
2. imported from neighbouring country/countries
3. imported from distant country/countries

Problems encountered

Occurrence

1. very frequent
2. occasional, but important
3. rare

Pharmacopoeial non-compliance

1. identification
2. assay
3. purity tests
4. other pharmacopoeia! test(s)

Organoleptic

1. change of colour
2. visible changes, i.e. capping, cracking, foam
3. inhomogeneous appearance
4. crystallization
5. particles, turbidity, precipitation
6. sedimentation, caking, agglomeration
7. smell, i.e. gas formation
8. rancidity
9. phase separation of emulsion
10. interaction with packaging material
11. other (please state)

Microbial

1. microorganisms visible
2. tests for bacteria positive
3. tests for fungi positive
4. tests for pyrogens positive
5. other (please state)

Additional information

.....

.....

.....

Date

Instructions

1. The answer sheet is to be completed for drug products mentioned in the following list of essential drugs for which you have experienced stability problems:

acetylsalicylic acid
aminophylline
ampicillin

benzylpenicillin

chloramphenicol
chloroquine
chlorpromazine

epinephrine
ergometrine
ethinylestradiol

glyceryl trinitrate

ibuprofen
indometacin
isosorbide dinitrate

methyldopa

nifedipine

paracetamol
phenoxymethylpenicillin
propranolol

spironolactone
sulfamethoxazole + trimethoprim
suxamethonium bromide

tetracycline
thiamine

warfarin

2. A separate answer sheet should be completed for each of the above preparations in a specific finished dosage form, e.g. one for tetracycline capsules and another for tetracycline ointment.

   Also applicable for other categories such as packaging material, source of drug product, etc.

3. Climatic zones (Schumacher P. Aktuelle Fragen zur Haltbarkeit van Arzneimitteln. [Current questions on drug stability.] Pharmazeutische Zeitung, 1974, 119:321-324):

   zone I - temperate
   zone II - subtropical with possible high humidity
   zone III - hot and dry
   zone IV - hot and moist.

Appendix 2
Stability testing: summary sheet

An example of a form in which the results of stability testing can be presented is shown below. A separate form should be completed for each pharmaceutical preparation tested.

Accelerated/real-time studies

Name of drug product
Manufacturer
Address

Active ingredient (INN)
Dosage form
Packaging

Batch number	Date of manufacture	Expiry date
1.....	../.../19	../.../19
2.....	../.../19	../.../19
3.....	../.../19	../.../19

Shelf-life ... year(s) ....month(s)

Batch size	Type of batch (experimental, pilot plant, production)
1.....	.....
2.....	.....
3.....	.....

Samples tested (per batch) .....

Storage/test conditions:
Temperature ...°C Humidity ... %
Light ...cd

Results

1. Chemical findings

2. Microbiological and biological findings

3. Physical findings

4. Conclusions

Responsible officer. . . . . .Date . . /. . /19