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Geneva, 28 November – 2 December 1994

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1. Introduction

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 28 November to 2 December 1994. The meeting was opened on behalf of the Director-General by Dr F. S. Antezana, Assistant Director-General, who emphasized the comprehensive role of the Expert Committee in dealing with a wide range of issues relating to the overall quality assurance of pharmaceutical products. In addition to the important task of elaborating and updating appropriate specifications for *The international pharmacopoeia,* he drew attention to other areas of the Expert Committee's work intended to assist WHO's Member States, especially developing countries. These included strengthening the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, advice on the establishment and management of drug testing laboratories, and recommendations on the function and structure of a small drug regulatory authority.

In May 1994, the World Health Assembly adopted resolutions WHA47.11-WHA47.17 related to drugs and pharmacy. It reaffirmed the principles embodied in the Expert Committee's documents concerning the role and functions of a small national drug regulatory authority and the WHO Certification Scheme, and approved the text on good manufacturing practices. It also requested the Director-General to continue the normative activities that provided standards to assure the quality, safety and efficacy of pharmaceutical and biological products. In this context, Dr Antezana drew attention to the complex issue of the registration of multisource products. He was confident that the Expert Committee would be able to offer advice in what was an area of great importance to many national drug regulatory authorities.

The Committee confirmed that the overall objective of its broad range of activities was to provide a foundation on which Member States could build a comprehensive approach to the quality assurance of pharmaceutical products. It believed that its role was to provide Member States with a technically sound but flexible model to serve as both a target and a framework for their regulatory activities. Member States would, of course, need to adapt specific elements of that model to local circumstances. A step-by-step approach to the implementation of individual guidelines was frequently advisable. Proper allowance could then be made for the stage of development of a particular regulatory system and the locally determined needs and priorities. The Committee emphasized that the aim was to assist Member States to develop an appropriate and sustainable quality assurance infrastructure in order to optimize the use of available resources. International and regional organizations should be encouraged to provide appropriate local training on the implementation of WHO guidance (developing strategies, adapting guidelines) and assistance in operating WHO schemes.

2. *The international pharmacopoeia* and related activities

2.1 Quality specifications for drug substances and dosage forms

The Committee was pleased to be informed that Volume 4 of *The international pharmacopoeia* had been published in English in 1994 and recommended that every effort should be made to expedite publication in other official languages of WHO since this would greatly enhance its usefulness. That it was widely used was evident from the preliminary response received to the user questionnaire. The Secretariat was encouraged to continue to collect and analyse information on the use of *The international pharmacopoeia* in order to target the specification work more precisely.

The Committee considered monographs on a range of drug substances, medicinal gases, and tablets, and recommended their inclusion in future volumes. It suggested that, to avoid delays in making approved texts available, more frequent publication of smaller collections of monographs should be considered.

Progress was noted on the preparation of additional monographs for substances on the WHO Model List of Essential Drugs (*1*) and for the associated dosage forms. The Committee confirmed the principle of paying due regard to the toxicity of the reagents specified in tests as mentioned in its twenty-ninth report (*2*) and in Volume 3 of *The international pharmacopoeia* (*3*).

2.2 Test methodology

With respect to dissolution testing, the Committee approved the text describing the basket and paddle methods for inclusion in *The international pharmacopoeia*. In view of the considerable number of comments received, consultation on the accompanying advisory notes would need to be extended. A careful approach would be adopted, however, in incorporating dissolution requirements in the individual monographs for tablets and capsules in *The international pharmacopoeia*. Any further considerations should be based on comparative information on published specifications compiled by the Secretariat.

Following consideration of a preliminary discussion text, the Committee agreed that inclusion of a test for bacterial endotoxins was appropriate for *The international pharmacopoeia*. It advised, however, that finalization of such a text should await the outcome of current initiatives being pursued within national and regional pharmacopoeial programmes with respect to the reference endotoxin and the methodology. It was hoped, in particular, that it might thus be possible to extend the method to accommodate lysates from the various species of organism used in different geographical regions of the world. Meanwhile, the Committee wished to encourage the in-house use of bacterial endotoxin testing in

place of the rabbit test for pyrogens whenever a suitable bacterial endotoxin test had been demonstrated to be satisfactory for a particular product.

As regards the useful discussion document prepared by the Secretariat on the microbial contamination of pharmaceutical products that were not required to be sterile, the Committee recommended that work on this important aspect of product quality should be pursued and concrete proposals presented at its next meeting.

Recognizing that a readily applicable means of evaluating the particulate contamination of injectable preparations was a high priority for *The international pharmacopoeia*, the Committee encouraged the Secretariat to continue the development of requirements based on the visual inspection method currently under consideration by the European Pharmacopoeia Commission.

2.3 International Nonproprietary Names for pharmaceutical substances

The Committee was informed of the current activities of the programme on International Nonproprietary Names (INNs) for pharmaceutical substances (*4*). It endorsed the "Guidelines for the graphic representation of chemical formulae" that had been prepared (Annex 1), which would promote harmonization in the presentation of structural formulae.

2.4 International Chemical Reference Substances and International Infrared Spectra

2.4.1 *Establishment of reference substances*

Fourteen new International Chemical Reference Substances[1] were adopted by the Committee according to the procedure described in the thirty-second report (*5*). It was noted that the stock of the previously established Reference Substance 4-epitetracycline ammonium salt was depleted and that it had been replaced by 4-epitetracycline hydrochloride.

The total collection now comprises 166 International Chemical Reference Substances and 12 Melting Point Reference Substances (Annex 2).

The Committee was interested to see the preliminary information concerning the use of Reference Substances that had been gathered from the user questionnaire, and suggested that the WHO Collaborating Centre for Chemical Reference Substances should pursue these enquiries. It

[1] Amodiaquine hydrochloride, bacitracin zinc, beclometasone dipropionate, dexamethasone phosphoric acid, dexamethasone sodium phosphate, dopamine hydrochloride, framycetin sulfate, (-)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine, liothyronine sodium, neamine hydrochloride, probenecid, pyrantel embonate, spectinomycin hydrochloride, vincristine sulfate.

would be especially important to clarify the extent to which Reference Substances were used directly as working standards rather than as intended, i.e. as primary standards to calibrate local working standards. It was also suggested that this aspect of their use should be brought to the attention of those ordering Reference Substances.

The Committee expressed its appreciation to the WHO Collaborating Centre for Chemical Reference Substances for its work and to the National Corporation of Swedish Pharmacies for its continued financial support for the WHO programme on International Chemical Reference Substances.

2.4.2 *Infrared reference spectra*

Further to the spectra established at the Committee's previous meeting, it adopted six additional International Infrared Reference Spectra.[1] Those listed in Annex 3 are now available from the WHO Collaborating Centre for Chemical Reference Substances, Stockholm, Sweden. It was noted that a number of additional infrared spectra are currently being validated. Precise instructions for the preparation of spectra are provided with each reference spectrum. Recommendations for the preparation and use of infrared spectra in pharmaceutical analysis, which will accompany the reference spectra, were approved by the Committee (Annex 4).

The WHO Collaborating Centre for International Infrared Reference Spectra, Zurich, Switzerland, which is responsible for preparing the Reference Spectra, had proposed that spectra should in future be recorded with both dispersive and Fourier transform infrared (FTIR) spectrometers in order to take into account the current availability of FTIR spectrophotometric equipment. This proposal was endorsed by the Committee. It would be the responsibility of those ordering spectra to state the type required. To facilitate the exchange of data and their use in computer spectral searches, the Committee proposed that the FTIR spectral computer files should be stored in the format recommended by the Joint Committee on Atomic and Molecular Properties.

3. Simple test methodology

The Committee noted the progress made in the development of tests additional to those already published by WHO in *Basic tests for pharmaceutical substances* and *Basic tests for pharmaceutical dosage forms* (*6, 7*). It recommended that these publications should be made available in all of WHO's official languages since that would significantly increase their usefulness. The Committee emphasized that

[1] Colchicine, erythromycin stearate, glibenclamide, salbutamol, salbutamol sulfate, sulfadoxine.

these tests had been designed specifically for use where reagents and equipment needed to be kept to a minimum. Reagents that were unstable, corrosive, expensive or difficult to obtain were therefore excluded. The Committee approved the publication of those tests that had been finalized and offered some suggestions on how to accelerate the verification process. It recommended that, to avoid delays in making information on tests available, more frequent issuing of collections of tests should be considered. It suggested that the scope of the next publication on basic tests should be extended to include additional information on, and references to, other simple test methodologies. The discussion paper on analytical considerations in pharmaceutical regulation (*8*) would serve as a valuable introduction to such a supplementary section. The Committee was conscious of the need to take into consideration the different priorities and stages of development of national drug control laboratories and assist them in making the best use of available resources.

The provision of advice and information on simple test methodologies complemented the Committee's work on pharmacopoeial specifications. While the latter were an essential part of the independent assessment of overall product quality, simpler tests were a valuable tool for primary screening, which could play an important part in detecting counterfeit and spurious products. As an example of appropriate, simplified analytical technology, the Committee endorsed the usefulness of the thin-layer chromatography (TLC) kits, reference tablets and associated materials (*9*) that had been evaluated in a number of WHO Member States.

4. Stability of dosage forms

4.1 Guidelines for the stability testing of pharmaceutical products containing established drug substances

The Committee considered a draft text on stability testing that had initially been prepared by the Secretariat and had subsequently been subject to wide consultation. Recognizing that stability testing represents the evaluation of a pharmaceutical formulation in its final container, the Committee agreed that the same fundamental approach should be adopted for all products irrespective of whether the active ingredient was an established drug substance. Where sufficient information was already available on the chemical stability of the active ingredient, however, this could be taken into account in designing simplified test protocols. Subject to some revision of the draft text so as to reflect this principle more clearly and to take into account the comments offered by the Committee, the guidelines were adopted (Annex 5). The availability of these guidelines was considered to be of special importance since they provided advice on the stability testing of products for use in the more extreme climatic conditions found in many developing countries. Such

advice was lacking in other guidelines, such as those formulated by the International Conference on Harmonisation (ICH).

4.2 Joint WHO/UNICEF study on the quality of selected drugs at the point of use in developing countries

Noting the preliminary results of this very useful study (*10*), the Committee expressed concern at the high apparent defect rate (up to 10.8%) among the small sample of products studied thus far. In addition to recommending more detailed analysis of the results obtained and an extension of the study, especially for the antibiotic formulations, the Committee suggested that as a goal a defect rate of no more than 1% would be consistent with adequate attention to product design and development, good manufacturing practices (GMP) and proper procurement and storage.

5. Good manufacturing practices for pharmaceutical products

5.1 Adoption of additional guidelines

The Committee adopted three annexes to supplement the main guidelines on good manufacturing practices (GMP) published as Annex 1 of its thirty-second report (*5*); these texts provided additional advice on the validation of the manufacturing processes (Annex 6), the manufacture of investigational products for clinical trials in humans (Annex 7), and the manufacture of herbal medicinal products (Annex 8).

5.2 Further guidance on good manufacturing practices

The Committee was pleased to note that further texts were in preparation on the manufacture of pharmaceutical excipients and the responsibilities of the "authorized person" as defined in the main guidelines. These texts would provide general advice suitable for inclusion in the GMP guidelines.

The Committee considered supplementary GMP guidance that had been prepared by the Children's Vaccine Initiative and considered by the WHO Expert Committee on Biological Standardization. The draft guidelines for the inspection of manufacturers of biological products would provide a good framework for inspections and should assist in clarifying certain aspects of GMP already dealt with in the main guidelines.

It was recommended that all such documentation should be brought together in a WHO compendium of GMP and related technical guidelines. Such a comprehensive collection of guidelines would be a very valuable tool. It would avoid the danger of fragmentation and offer an opportunity to harmonize the related texts.

6. Legal and administrative aspects of the functioning of national drug regulatory authorities

6.1 Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

In adopting these guidelines (Annex 9), the Committee noted the wide consultation that had taken place following the suggestions made at its thirty-third meeting (*11*). It was pleased to note that the guidelines had already been adapted for local use by a number of WHO Member States and that positive feedback had been received especially with regard to the flexibility and clarity of the guidance. They were designed to allow a step-by-step approach tailored to the stage of development of a particular registration system and the needs and priorities of the national health authorities. The guidelines were intended to assist drug regulatory authorities and international organizations involved in the procurement of pharmaceutical products, and to provide manufacturers with an indication of the data required. The Committee recognized that these guidelines were a first step: they would need to be supported by training and advice on implementation. Use by international organizations would be crucial to their promulgation. It recommended that further consideration should be given to the feasibility of developing a system of international reference products.

6.2 The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

The Committee adopted revised guidelines for implementing the expanded Certification Scheme (Annex 10). The proposed guidelines and associated forms published as Annex 3 of the Committee's thirty-second report (*5*) had been refined following field trials in a number of WHO Member States and discussion during the sixth and seventh biennial International Conferences of Drug Regulatory Authorities. The importance of the Scheme had been endorsed by the Forty-fifth World Health Assembly in resolution WHA45.29. In its revised form, the Scheme was intended to provide more rigorous control through a more effective exchange of authenticated information. The Committee emphasized that the extent to which the Scheme would meet its objectives would depend on the integrity with which it was operated by WHO Member States. It relied, *inter alia*, on exporting Member States fully meeting the criteria for eligibility, and on importing Member States basing all procurement activities on the Scheme. In the case of products manufactured exclusively for export, the certifying authority had to be satisfied that the quality standards were the same as those applied to products manufactured for sale in the exporting country.

The Committee considered ways in which WHO, in discussion with drug regulatory authorities, might take further steps to strengthen and promote

the Scheme. It was recognized that there was a need for more advice and training on the implementation of the Scheme by importing Member States.

A proper appreciation of the value of the Scheme in drug importation could be fostered most effectively by those in close contact with importing authorities. The active role of WHO in implementing the Scheme was acknowledged, and it was suggested that the results of a recent study of its use (*12*) should be used to target future WHO activity in promoting and supporting the Scheme. As a basis for discussion, the Committee suggested that all those using the Scheme should be encouraged to notify WHO of any problems. Complaints could then be investigated and information collated with a view to proposing possible sanctions, such as the notification of serious abuses of the Scheme to the World Health Assembly.

The Committee recalled that the certification of active pharmaceutical substances was covered by the expanded and revised version of the Certification Scheme as adopted by the Forty-first World Health Assembly in 1988 in resolution WHA41.18. It was informed that the proposals referred to in its thirty-third report would be developed as soon as the guidelines for finished products were finally adopted by the World Health Assembly for implementation.

6.3 Guiding principles for formulating national drug legislation

The Committee considered two draft texts providing guidance in the form of a model legislative scheme and a draft law for adaptation by small national drug regulatory authorities on the regulation of pharmacists and pharmacies. It concluded that such guidance would be of immediate value to the many countries still in the process of establishing drug regulatory and legislative systems. While other countries might also profit from such a framework, the Committee pointed out that authorities should always be cautious about changing systems and procedures that work effectively. The introductory notes to the two documents should be expanded so as to explain more clearly for whom the advice was intended and how it could be adapted to national needs. The Committee therefore recommended that work on such texts should be continued, and suggested that the drafts might be published in one of the WHO periodicals so as to widen the consultative procedure and be made available in several languages.

6.4 Role of the pharmacist

The Committee was informed that resolution WHA47.12 on the role of the pharmacist in support of WHO's revised drug strategy was adopted by the World Health Assembly in 1994 based on the reports of the two global WHO meetings held in New Delhi in 1988 and in Tokyo in 1993 (*13*). The Committee thanked the International Pharmaceutical

Federation (FIP) for drawing its attention to the text on good pharmacy practices (GPP) in community and hospital pharmacy settings as adopted by the FIP Congress in 1993 (*14*). The Committee welcomed the FIP initiative in so far as it provided a basis for the implementation of some of the principles embodied in resolution WHA47.12. However, if the text were to be endorsed by the Committee, it would need to be expanded so as to reflect current emphasis on the pharmacist's specific responsibility for assuring the quality of pharmaceutical products throughout the distribution chain. Particular attention would have to be paid to the current inadmissible prevalence of substandard and counterfeit products in some national markets.

6.5 Model legislative provisions to update national legal texts to deal with counterfeit drugs

The Committee, realizing the importance and timeliness of the issue, expressed its satisfaction that a preliminary text had been drafted to provide model legislative provisions for dealing with counterfeit drugs. It recommended that the draft should be circulated to experts, information officers and those concerned in interested nongovernmental organizations, who should be asked to comment on the technical and legal aspects. The importance of establishing a legally sound definition of "counterfeit drug" and related terms, as well as of giving advice on the possible regulatory actions to be taken in order to hinder market penetration by counterfeit drugs, was recognized.

6.6 Additional guidance

The Committee reviewed the "guidelines for the assessment of herbal medicines" issued by WHO as an unpublished document in 1991. It was noted that this text had been widely distributed to WHO Member States and discussed at the sixth International Conference of Drug Regulatory Authorities in Ottawa, Canada, in 1991. In recognition of its utility, the Committee adopted the text (Annex 11).

The Committee welcomed the recent publication of two manuals that endorse WHO's quality assurance strategy, namely the *FIP Guidelines for drug procurement* (*15*) and a new revised edition of *Management of drug purchasing, storage and distribution: manual for developing countries* (*16*), developed by the industrial pharmacists' section of FIP together with the German Pharma Health Fund e.V.

It also took note of the *Quality assurance management manual* prepared by the Department of Medical Sciences of the Ministry of Public Health of Thailand. The Committee considered that the principle of developing quality assurance manuals was valid not only for quality control laboratories but also for overall drug regulatory activities, and that the Thai manual, together with the draft guideline on quality system requirements for GMP inspectorates, prepared by the Pharmaceutical

Inspection Convention (PIC), could provide a basis for the development of national and/or international recommendations to strengthen the capabilities of drug regulatory authorities.

A number of WHO publications and documents on essential drugs were presented to the Committee for information.

6.7 Training activities

The Committee was informed of the wide diversity of training activities related to the functioning of national drug regulatory authorities in which WHO, through its Division of Drug Management and Policies, had been involved since the previous meeting of the Committee; these included the following:

- Training in the use of a model software package designed to support the drug registration process, developed by WHO with financial support from the German and Italian Governments. To date, this system has been installed and on-site training provided in over 20 WHO Member States. An important objective is to promote Technical Cooperation among Developing Countries by establishing training capacity within national authorities selected on a regional basis. Cuba, Guatemala, Tunisia, Venezuela, and Zimbabwe have been selected for this purpose.
- Regional and subregional courses on the administrative aspects of drug control organized by the German Foundation for International Development (DSE).
- Seminars on quality assurance cosponsored by WHO and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).
- Cosponsorship of, and participation in, the training of inspectors and drug regulators together with other WHO and United Nations programmes, notably WHO's Programme on Substance Abuse, the United Nations International Drug Control Programme, the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, and the WHO Action Programme on Essential Drugs.
- Initiation of training and collaborative activities for drug quality control laboratories particularly in the African Region.
- An intensive 12-month training course provided by the University of Bradford, England, intended primarily for pharmacists working in the public sector in developing countries and also for the newly independent states of the former Soviet Union.
- Training for inspectors in GMP in the WHO Collaborating Centre for Drug Information and Quality Assurance in Hungary; this is available on request.

In addition to the foregoing, the training scheme for analysts and inspectors working in drug regulatory authorities offered by the IFPMA

and by the World Federation of Proprietary Medicine Manufacturers (WFPMM) and coordinated by WHO through its Division of Drug Management and Policies continues to operate.

7. Quality assurance in the supply system

7.1 Guidelines on import procedures for pharmaceutical products

The Committee endorsed the guidelines on import procedures for pharmaceutical products contained in Annex 12, which have been developed through an extensive consultative procedure and take into account the needs of, and resources available in, developing countries. They are intended to provide a framework for the effective control of pharmaceutical products at specified ports of entry and also provide a basis for collaboration between the various interested parties.

7.2 Guidelines for inspection of drug distribution channels

The Committee noted the progress made in developing recommendations on inspection in the distribution system, and encouraged the Secretariat to continue consultations on this matter.

8. Terminology

The Committee noted that a collection of terms related to drug quality assurance, together with their definitions, had been prepared by WHO. The project on terminology harmonization was encouraged. However, it was felt that global harmonization of all related terms would be a very difficult task. A list of key terms, with definitions, would be helpful in standardizing the terminology used in WHO publications and documents. At a later stage, the translation of these key terms into other WHO official languages would facilitate the promotion and understanding of such materials.

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Annex 1
Guidelines for the graphic representation of chemical formulae

1. Introduction

1.1 Chemical names and structures must be portrayed correctly and unambiguously in pharmacopoeias and other compendia. For details of nomenclature conventions, readers are referred to the recommendations of the International Union of Pure and Applied Chemistry (*1, 2*).

1.2 These guidelines are intended to help scientists draw structural formulae correctly. They are only recommendations, however, because unwavering adherence to these principles is not always practicable. Thus, the guidelines should be followed closely wherever possible, but may be adapted, with certain exceptions, where necessary to produce accurately drawn structural formulae. Details of the formulae, such as bond lengths, the position of subscripts and superscripts, and the closeness of apposition of individual atomic symbols, will depend on the drawing method used, whether computer-based or manual.

1.3 Where possible, the structures are:
- set out horizontally rather than vertically;
- designed to be read from left to right; the highest-numbered atom in an acyclic structure should be on the left, the systematic numbering decreasing from left to right.

1.4 The numbering of rings is consistent with established chemical nomenclature. Where practicable, rings should be numbered in a clockwise direction.

1.5 Links between atoms and/or groups are represented by dashes. The structures should by and large be shown in full, with the complete rings. However, certain very common groups of atoms are shown in a more condensed form, as follows:

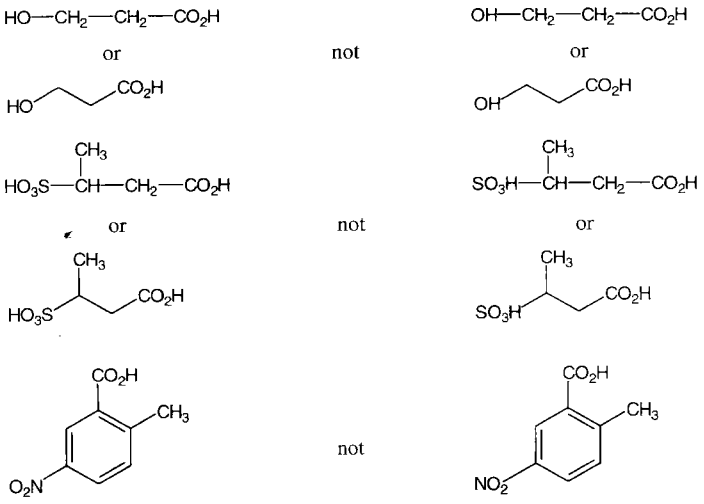
$-CH_3$ methyl	$-CHO$ formyl	$-CO_2H$ carboxy	$-CO_2^-$ carboxylate	$-CN$ cyano
$-NC$ isocyano	$-OH$ hydroxy	$-OCH_3$ methoxy	$-SO_3H$ sulfo	$-SO_3^-$ sulfonate
$-NH_2$ amino	$-NO_2$ nitro	$-N_3$ azido		

1.6 Symbols for groups of this kind, such as –Me, –Et, –Pr, –Ph, etc., are often used as a means of saving space.

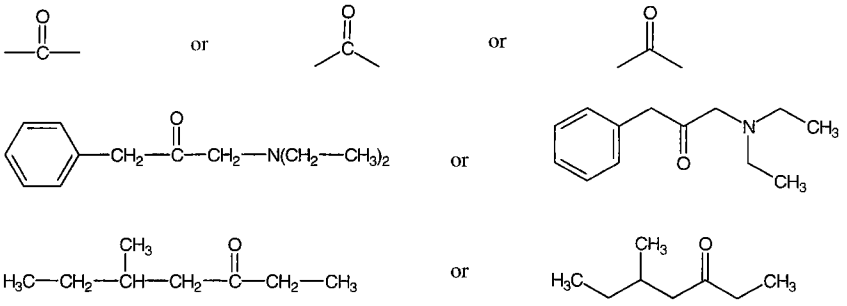
1.7 The bulky group *tert*-butyl (1,1-dimethylethyl) is often shown as $-C(CH_3)_3$. Hydroxymethyl and aminomethyl groups can be represented in either expanded or condensed form:

$-CH_2-OH$ or $-CH_2OH$ $\qquad$ $-CH_2-NH_2$ or $-CH_2NH_2$

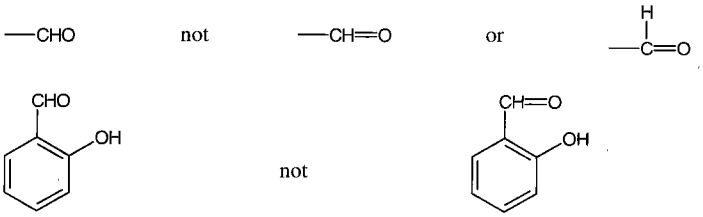
1.8 A polyatomic group is set out such that the atom that is directly attached to the rest of the structure is shown closest to the connecting dash:



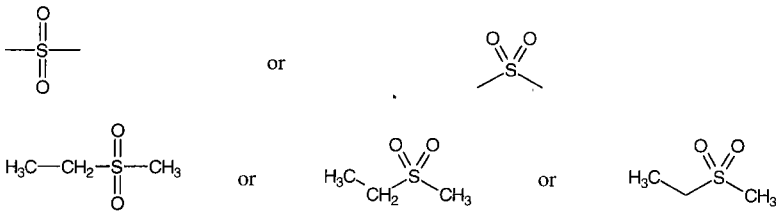
1.9 The carbonyl group in ketones is depicted as:



In aldehydes it is depicted in the condensed rather than expanded form:

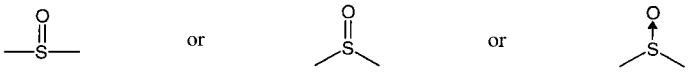


1.10 The sulfonyl group is depicted as:

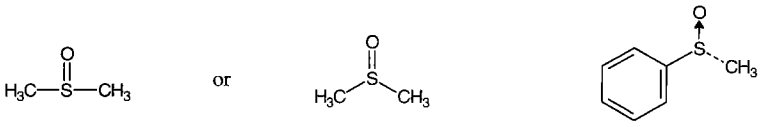


rather than in the condensed form —SO_2—

The sulfinyl group is shown as:



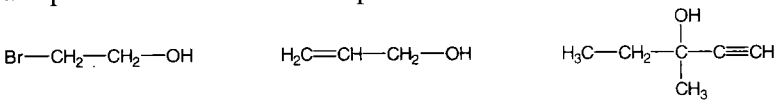
rather than in the condensed form —SO—; the last representation is useful as a means of recognizing a chiral compound:



2. Acyclic structures

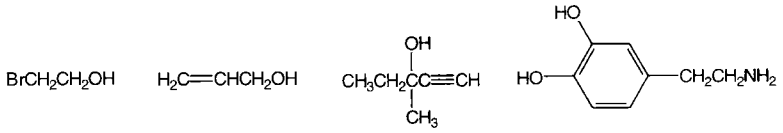
2.1 In acyclic structures, a single bond is shown as a dash, unless a broken line, a wedge or a wavy line is used to depict stereochemistry,[1] a carbon-

carbon or carbon-heteroatom double bond is shown as double dash, and a triple bond is shown as a triple dash:

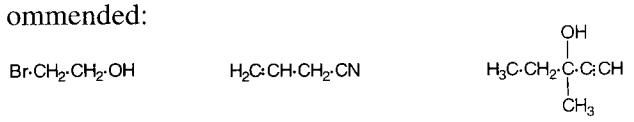


2.2 In computer-aided drawing, because it takes time to insert dashes, a single bonding dash between the atoms of an aliphatic chain need not be used. Nevertheless, in this compact form:

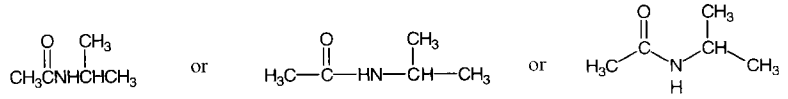
- a dash is used to show a single bond between a substituent and a chain or between a chain and a ring;
- a double dash and a triple dash are used to show a double bond and a triple bond respectively;
- dashes, broken lines or wedges are used to depict stereochemistry.[1]



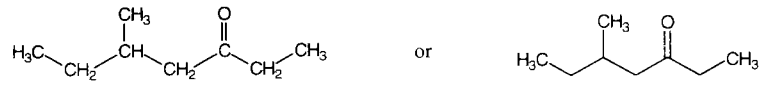
Sometimes dashes are replaced by dots, but this practice is not recommended:



2.3 Acyclic chains can be represented either in linear way or in the form of lines at an angle to one another; the latter option is preferred because it sometimes makes it easier to show an atom next to the atom to which it is linked and offers a better configuration for structures having chiral centres (see section 7):



The latter representation may be simplified by omitting the letter "C" from the central skeleton and the letter "H" for hydrogen atoms, which can be understood to be present. The carbon chain is then represented by a series of lines at an angle to one another, with all terminal groups set out in full:

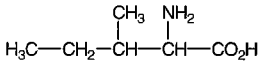


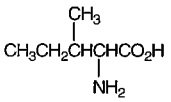
This form of representation is particularly useful for drawing long carbon chains and is often used in chemical literature. Moreover, this is the form that computer drawing programs are designed to use.

[1] A bond that lies below the plane of the paper is shown by a broken line, one that lies above that plane by a wedge, and one whose configuration is not known by a wavy line.

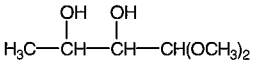
2.4 The groups at the left-hand end of the formula are always inverted, except in the compact form without dashes.

2.5 Single substituents (whether mono- or polyatomic) are not shown in parentheses and included in the structure, but are linked to it with dashes:


not $H_3C—CH_2—CH(CH_3)—CH(NH_2)—CO_2H$


not $CH_3CH_2CH(CH_3)CH(NH_2)CO_2H$

2.6 When several identical groups are linked to the same atom, they are often shown in parentheses, a subscript on the right indicating their number; dashes are not used to show bonding in this case: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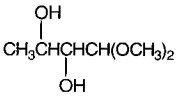
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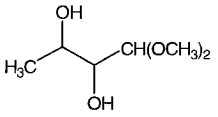

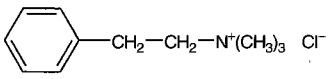
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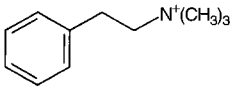
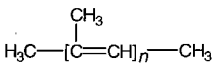


$[(H_3CO)_2CH]_2NH$ $(HO—CH_2—CH_2)_3N$ or $(HOCH_2CH_2)_3N$

2.7 In acyclic chains that contain a large number of identical groups, such groups can be placed in square brackets, their number being indicated by a susbscript on the right:

$H_3C—[CH_2]_4—CO_2H$ or $CH_3[CH_2]_4CO_2H$ 

In general, the points of bonding between adjacent repeated groups are not shown, but there are situations in which they may be indicated to avoid ambiguity (see section 15).

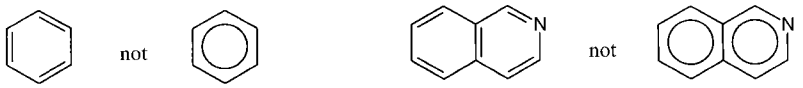
2.8 In a polymethylene chain, when one extremity is linked to a heteroatom, the methylene group linked to that heteroatom may be left outside the brackets if a contracted group such as hydroxymethyl, aminomethyl, etc., is to be shown:

$H_3C—[CH_2]_5—CH_2OH$ $H_3C—[CH_2]_4—CH_2NH_2$

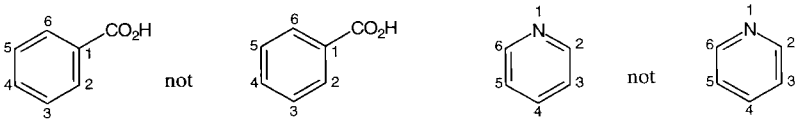
3. Cyclic structures

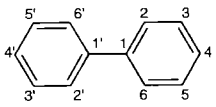
3.1 Rings are shown in full as polygons. The symbols of the carbon atoms that form the ring are not shown, but are represented by the vertices of the rings. The hydrogen atoms attached to them are not represented unless they are needed to show stereochemistry. The symbols of atoms other than carbon are shown with all the hydrogen atoms attached to them but without linking dashes. Single, double or triple bonds are indicated thus:

3.2 In aromatic systems a circle should not be used to depict delocalized electrons; instead, alternating single and double bonds are shown (Kekulé representation):



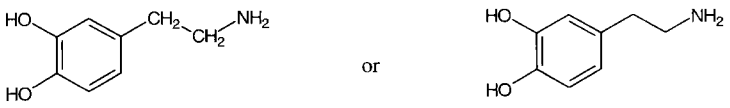
In monocyclic aromatic compounds, double bonds should be arranged to have the lowest possible numbering:



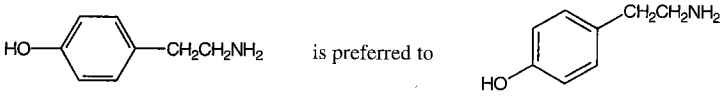


3.3 In fused polycyclic systems a double bond should form the fusion bond nearest to the right-hand side:

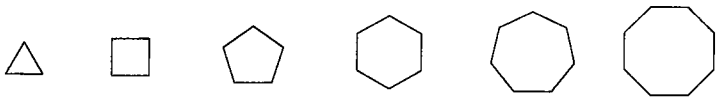
3.4 Six-membered rings should be represented with a vertex at the base rather than a horizontal bond when the chains linked to them are represented in the form of lines at an angle to one another (as is preferred for acyclic chains – see section 2.3):



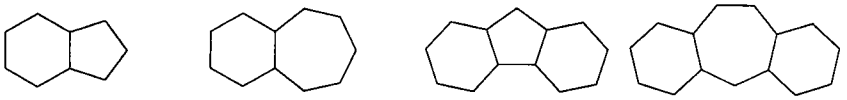
3.5 Depiction of the ring with a horizontal bond at the base is, however, preferred when the chains are shown in the compact form:



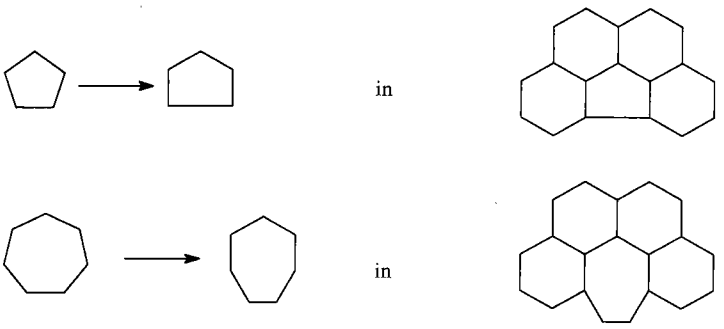
3.6 Rings are shown as regular polygons when they consist of up to eight atoms:



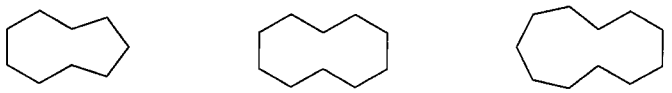
3.7 Wherever possible, the regularity of the polygons is maintained in the drawing of fused cyclic compounds:



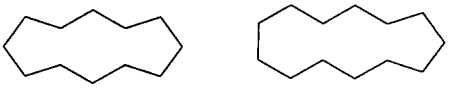
3.8 However, in fused polycyclic systems the polygons may often be distorted in order to maintain the symmetry of the structure:



3.9 Rings with more than eight vertices are often shown with re-entrant angles. It is recommended by Chemical Abstracts Service (CAS) that they should be drawn like amalgamated rings with five, six or seven vertices:

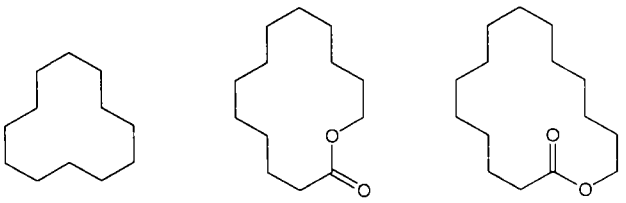


9 10 11



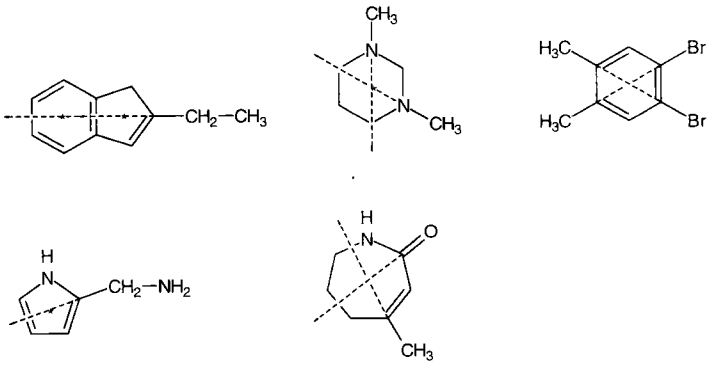
12 13

3.10 These recommendations need not always be followed. In particular, the shape of such large rings as those of macrolide antibiotics is often determined by the presence of more or less bulky substituents and the need to indicate stereochemical conformations:

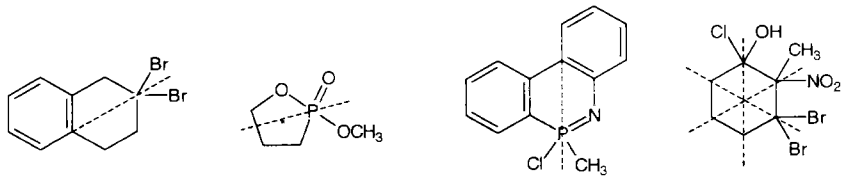


12 14 16

3.11 When a substituent is attached to an atom occupying a position in a ring (carbon or heteroatom), the direction to be taken by the dash linking it to that atom can be found by extending the line bisecting the cycle:

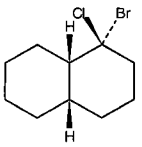


3.12 Where two substituents are attached to the same ring atom, they should generally both be at the same angle to the bisector, and preferably at a right angle to the adjacent side:

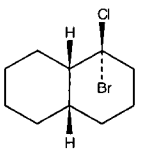


However, for the graphic representation of certain structures, such as steroids, other considerations may have priority.

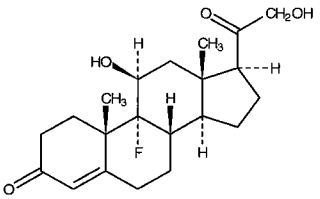
3.13 Substituents are normally placed outside rings, except in steroids, terpenes and alkaloids (see sections 9, 10 and 12) and where substituents attached at bridgeheads can only be displayed inside the rings of polycyclic structures:



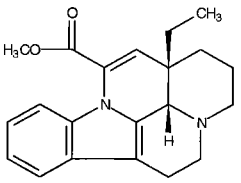
not



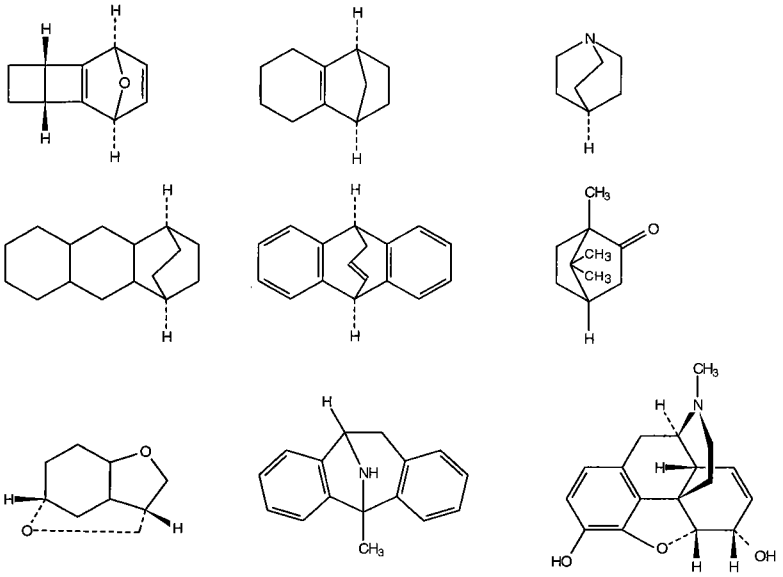
but



or

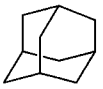


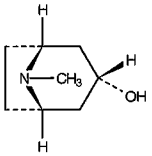
3.14 In bridged structures, a non-atomic bridge (direct bond) is represented by a straight line, an atomic bridge by lines at an angle to one another. The symbols for carbon atoms are not shown; however, if the bridge contains one or more heteroatoms, the atomic symbols for those atoms are shown. To give some perspective to the figure or to represent stereochemical features, wedges, thickened lines or broken lines can be used (see p. 19):



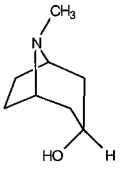
3.15 Sometimes a three-dimensional approach is possible, if a planar representation is considered not clear enough:

or





or



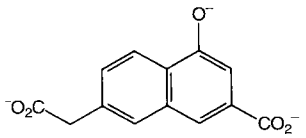
4. Ionic structures

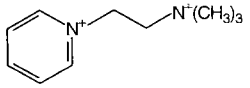
4.1 In general, in ionic structures, the cationic part is placed on the left and the anionic part on the right.

4.2 Ionic charges are not encircled and are shown as superscripts on the right of the charged atom. Multiple charges are indicated by writing *n*+ or *n*– and not by writing the + or – symbol *n* times.

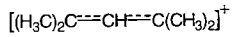
4.3 A terminal charge is shown as a superscript on the right of the group concerned, unless the order of atomic symbols in the group is reversed, when the charge is shown as a superscript on the left. In a lateral acyclic chain, if there is no space for a superscript on the right of the atom concerned, the charge can be shown immediately above that atom. When a ring is involved, the charge is usually placed outside the ring. When it is difficult to place the charge without ambiguity, it may be shown inside the ring:

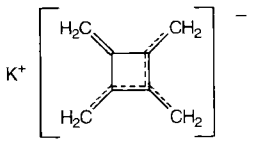
Na^+ Al^{3+} Cl^- SO_4^{2-}

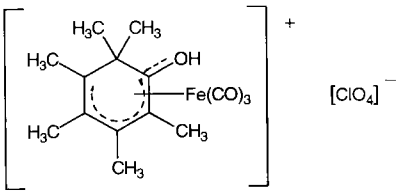




4.4 In structures with delocalized charge, the structure is put in square brackets, with the charge sign outside them as a superscript on the right:





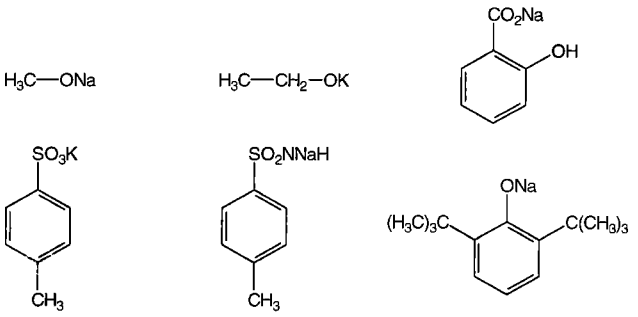


4.5 Metal salts of inorganic acids are shown without charges or bonds. If they include several metals, the symbols for the metals are shown in alphabetical order. In acid salts, the metal precedes the hydrogen. Molecules of water of crystallization or of substances of solvation follow the formula of the salt, from which they are separated by a comma:

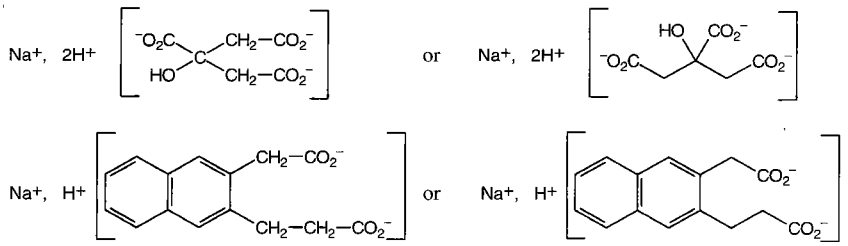
$NaBr$ $NaHCO_3$ $AlK(SO_4)_2,12H_2O$ $NaH_2PO_4,2H_2O$ $AlCl_3,4C_2H_5OH$

For inorganic compounds, centred dots are recommended by the International Union of Pure and Applied Chemistry (*2*). However, several pharmacopoeias have for a long time been using the comma for both organic and inorganic compounds.

4.6 In the metal salts of organic acids and the metal compounds of alcohols, phenols (and their sulfur, selenium and tellurium analogues), amines and amides, the metal symbol usually replaces the "acid" hydrogen, but neither charges nor bonds are shown:

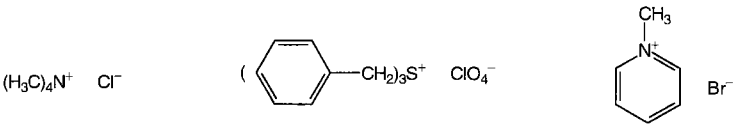


Nevertheless, ionic forms may be used when substances contain several "acid" groups to which the various cations cannot easily be attributed:



4.7 Amine salts are shown with the structure of the amine on the left and, after a comma, the formula of the acid on the right:

4.8 Quaternary ammonium salts and other compounds with a positive charge on a heteroatom (P, As, Sb, O, S, Se, Te) are shown in ionic form (with + and – charges), the two ions being separated by a space:

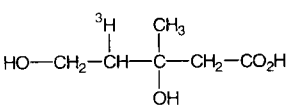


4.9 In inner salts, the positive and negative charges are shown and are normally placed in the structure as recommended above:

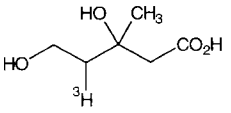
5. Isotopically modified compounds

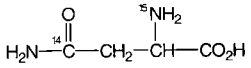
5.1 In an isotopically modified compound, the isotope used is indicated by its mass number placed as a superscript on the left of the symbol of the element concerned. Deuterium and tritium are written ^{2}H and ^{3}H respectively. The carbon atom in a ring or in a simplified angular-chain representation is explicitly designated when its mass number is shown:

$Na^{131}I$ $Na_2H^{32}PO_4$ ^{99m}Tc

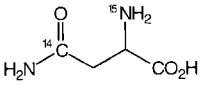


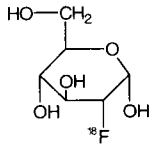
or

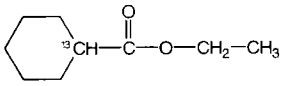




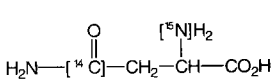
or

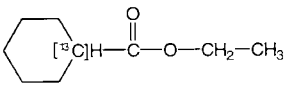






5.2 When atomic symbols in formulae are drawn without square brackets (as above) the compounds are assumed to be isotopically substituted, i.e. the atom concerned is completely replaced by the nuclide shown. To indicate isotopic labelling (partial replacement of the atom by the nuclide shown), atomic symbols in formulae should be in square brackets:





6. Coordination compounds

Non-cyclic structures

6.1 According to current usage (*1*), in a non-cyclic structure, the symbol of the central atom is placed on the left and is followed by the ionic ligands and then by the neutral ligands. Polyatomic ligands are placed in parentheses, with the atom linked to the central atom on the left. If several identical ligands are attached to the central atom, their number is indicated as a subscript to the right. In each class of ligands, the symbols of the linking atoms, and then of any other atoms, are shown in alphabetical order. The complete formula of the coordination entity (neutral group or complex ion) is placed in square brackets.

6.2 The individual charges usually carried by the central atom and the ligands are not normally shown; they may, however, be shown in structural formulae when it is difficult to show all the coordination links.

6.3 If the entire structure consists of ions, the positive ions are placed on the left and the negative ions on the right, the number of each being indicated as a subscript to the right. No spaces should be left between representations of ionic species within the formula of a coordination compound. If the charge of a coordination entity needs to be specified, it is placed outside the square bracket as a right superscript:

$Na_2[Fe(CN)_5(NO)]$ $Li_2[Zn(CH_3)_6]$ $[CoCl(NO_2)(NH_3)_4]Cl$

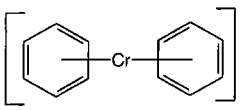
$[CoCl_2(NH_3)_4]Br$ $[Co\{SC[N(CH_3)_2]_2\}_4](NO_3)_2$ ion $[Fe(CN)_6]^{3-}$

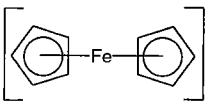
Cyclic structures

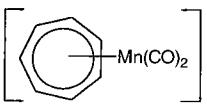
6.4 The rings follow the conventions for cyclic compounds. Where possible, the metal atom is placed in the centre of the group. Square brackets are placed round every coordination entity containing one or more rings, even if the charge is zero.

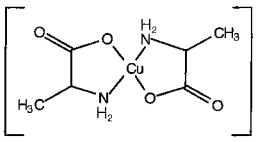
6.5 "Sandwich" structures are shown with the rings connected to the central atom by a line starting from inside the cycle and passing through one side.

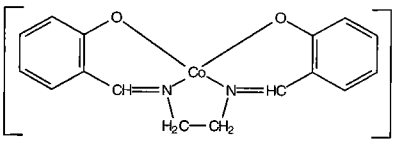
6.6 Benzene rings and condensed benzene systems in "sandwich" compounds are drawn with alternating single and double bonds. Pentagonal and heptagonal rings are shown with a circle inside:











Stereochemistry

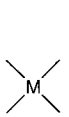
6.7 The stereochemistry of mononuclear complexes is expressed by means of special descriptors. The first of these is the "system indicator" formed from an abbreviation for the central atom geometry and the coordination number.

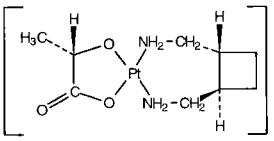
6.8 *T-4: tetrahedral complexes.* Described by the chirality symbol (*R*) or (*S*), they are shown in the same way as chiral carbon atoms, a broken line

denoting a bond projecting behind the plane of the paper and a filled wedge one projecting in front of that plane:

or

6.9 *SP-4: square planar complexes.* The four coordination links are shown in the plane of the paper:

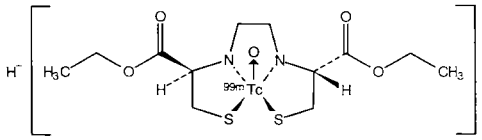




lobaplatin

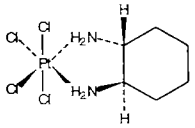
6.10 *TBPY-5: trigonal bipyramidal complexes.* The reference axis is shown in the plane of the paper; of the three other ligands, one is assumed also to be in the plane of the paper, one in front of it and the other behind it:

6.11 *SPY-5: square pyramidal complexes.* The reference axis with its lone coordinating atom is shown in the plane of the paper and four coordination links are assumed to be in a plane perpendicular to the reference axis, two in front and two behind the plane of the paper:



technetium (^{99m}Tc) bicisate

6.12 *OC-6: octahedral complexes.* Two coordination links are shown as the axis in the plane of the paper and four are assumed to be in a plane perpendicular to the reference axis, two in front and two behind the plane of the paper:



ormaplatin

6.13 *PBPY-7: pentagonal bipyramidal complexes.* Two ligands are shown attached to the extremities of an axis in the plane of the paper; the five other coordination links are shown as their projection on to the plane perpendicular to this axis:

7. Stereochemistry

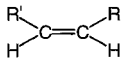
7.1 As already mentioned, a broken line denotes a bond projecting behind the plane of the paper and a filled wedge one projecting in front of that plane. A line of normal thickness denotes a bond lying in the plane of the paper. Hatched lines are sometimes used instead of broken lines. The practice of using a reversed wedge instead of a broken line for a bond projecting behind the plane of the paper is not recommended. In complicated structures, the dashes can be lengthened, shortened or displaced if necessary.

7.2 Hydrogen is represented by its symbol "H" whenever a configuration has to be shown.

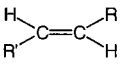
Geometric isomerism

7.3 For compounds containing double bonds it is customary to draw the formula so that the reference plane of the double bond is perpendicular to that of the paper; the bonds whereby atoms are attached directly to the doubly bonded atoms lie in the plane of the paper and are depicted with lines of normal thickness.

7.4 Isomers are shown with the two sequence-rule-preferred atoms or groups (each attached to one atom of the double bond) placed on the same side of the reference plane for the (*Z*)-isomer and on the opposite side of this for the (*E*)-isomer:

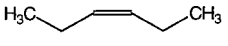


(*Z*)

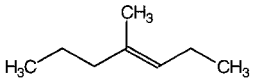


(*E*)

7.5 In simplified carbon chains depicted by lines at an angle to one another, the hydrogen, if any, may be omitted (see sections 10 and 11):

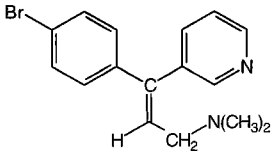


(*Z*)

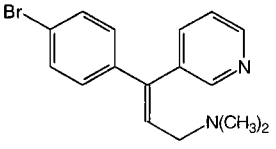


(*E*)

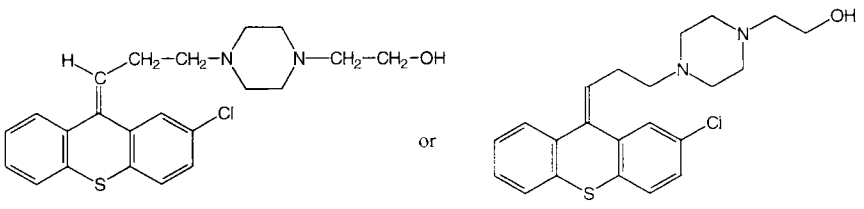
Examples of (*Z*)-compounds:



or

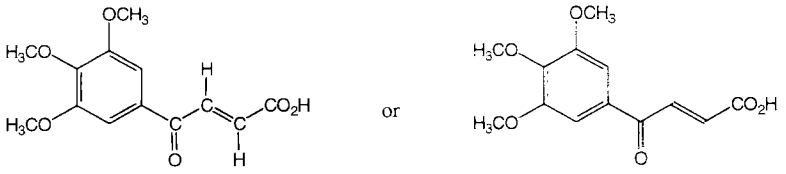


zimeldine

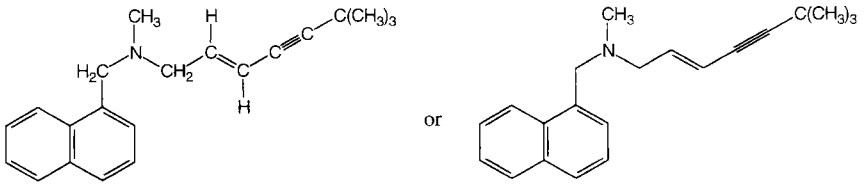


zuclopenthixol

Examples of (*E*)-compounds:



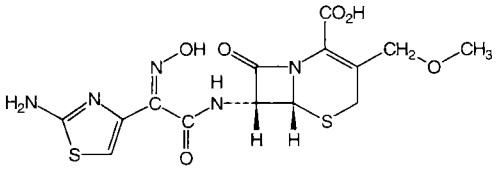
baxitozine



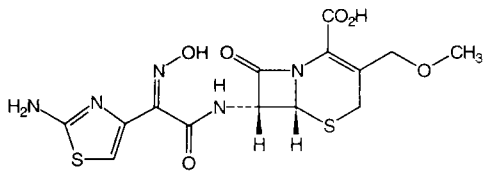
terbinafine

(Note that the two bonds attached to the carbons of the triple bond are drawn in a straight line.)

7.6 The same conventions are used for the isomers of oximes:

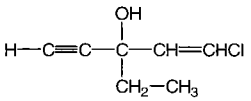


or



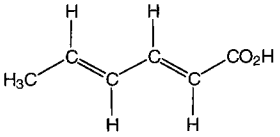
cefdaloxime (*Z*)

7.7 If the stereochemistry relative to the double bond is not specified a linear representation may be useful:

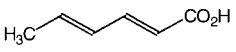


ethchlorvynol

7.8 The same conventions are used for compounds with several double bonds:



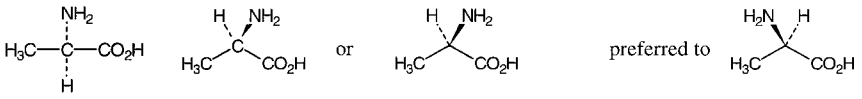
or



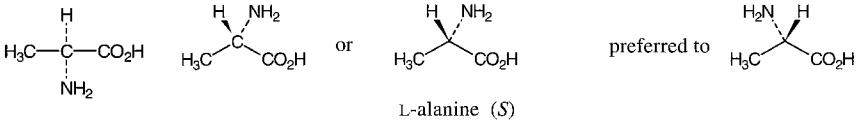
sorbic acid (*E,E*)

Compounds with one centre of asymmetry

7.9 In acyclic compounds with one centre of asymmetry, the general conventions can be used to represent each isomer either as a linear structure or with lines at an angle to each other (if possible, the larger "condensed" groups should be on the right, for aesthetic reasons).



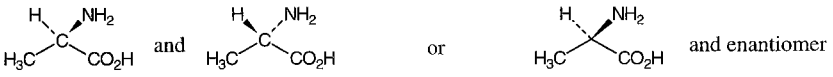
D-alanine (*R*)



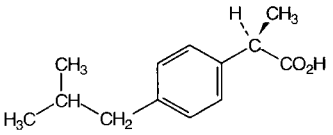
L-alanine (*S*)

(International Nonproprietary Names apply, by definition, to the L-form.)

7.10 The racemate can be represented by showing both isomers side by side or, more simply, showing only the (*R*)-isomer followed by the legend "and enantiomer".

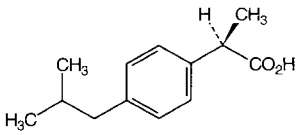


DL-alanine (*RS*)



and enantiomer

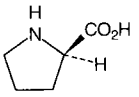
or



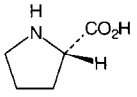
and enantiomer

ibuprofen

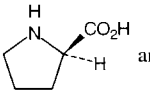
7.11 Similar representations are used for cyclic compounds with one centre of asymmetry:



D-proline (*R*)



L-proline (*S*)

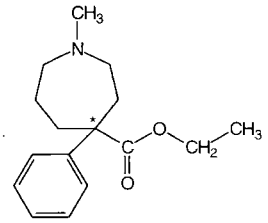


and enantiomer

DL-proline (*RS*)

(International Nonproprietary Names apply, by definition, to the L-form.)

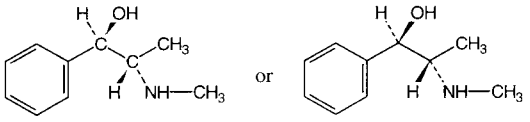
7.12 If the chirality of the centre is unknown or not specified, the bonds joining atoms or groups to the chiral atom are shown as lines of "normal" thickness. The use of a star or asterisk to identify the chiral centre may be useful:



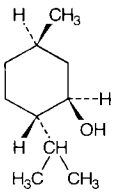
ethoheptazine (not specified)

Compounds with several chiral centres

7.13 In compounds containing several centres of asymmetry, the same conventions apply to each of these centres:



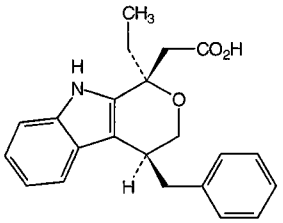
ephedrine (1*R*.2*S*)



levomenthol

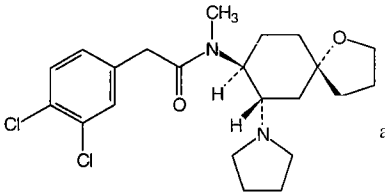
7.14 The racemates (racephedrine and racementhol respectively) are depicted by the same structures followed by the legend "and enantiomer", rather than by showing the two isomers side by side.

7.15 The same conventions are used for *cis-trans* isomerism relative to a planar (or approximately planar) ring:



and enantiomer

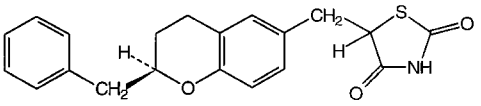
pemedolac (±)-*cis*



and enantiomer

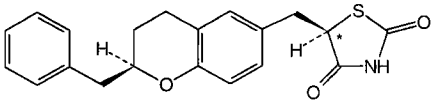
spiradoline (±)-(5*R**,7*S**,8*S**)

7.16 Mixtures of epimers are often shown by using the "normal" dashes at the epimeric centre (see also section 11):



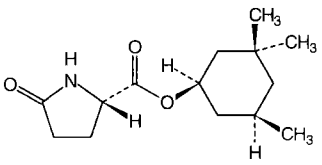
englitazone

However, the substance is preferably represented by showing the (*R*)-isomer at the epimeric centre, placing an asterisk near this C atom and adding the legend "and epimer at C*":

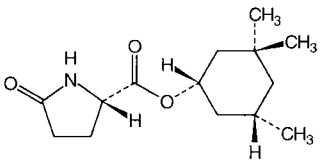


and epimer at C*

7.17 In more complicated cases, it is better to draw each component of the mixture so as to show all the pecularities of the structure:



and

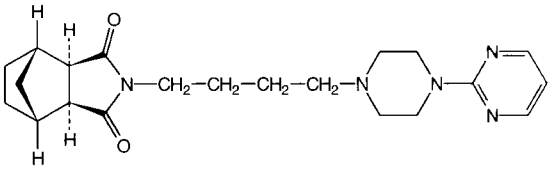


crilvastatin : (±)-*cis* only for the cyclohexane ring

Isomerism of fused rings

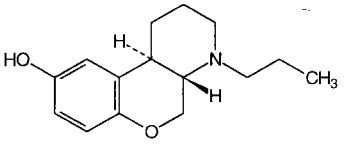
7.18 In polycyclic compounds, the atoms or groups attached at saturated bridgeheads common to two rings are shown by their symbols so as to indicate the stereochemistry resulting from the way that the cycles are fused.

The *cis*-isomer is depicted with the bonds shown either both as wedges or both as broken lines:



tandospirone

The *trans*-isomer is depicted with one of the bonds as a wedge and the other as a broken line:

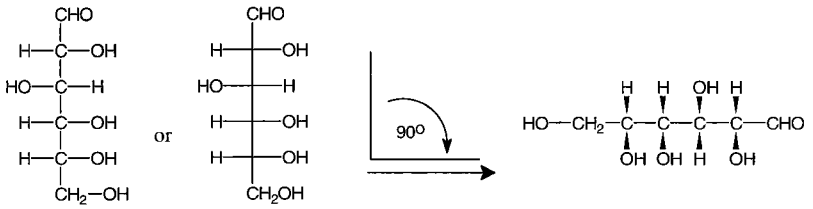


and enantiomer

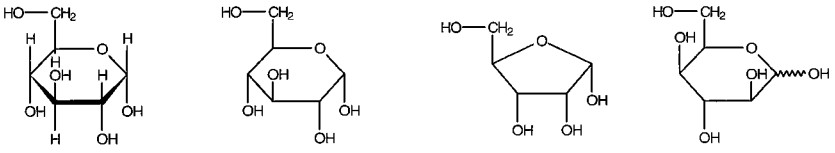
isomolpan

8. Carbohydrates

8.1 The Fischer projection is used to depict the acyclic forms of monosaccharides: the chain is shown vertically with carbon-1 on top and the horizontal bonds from carbon-2 to the penultimate carbon atom are assumed to be oriented towards the observer. This representation may be simplified by omitting the letter "C" in the central chain. The formulae are sometimes set out horizontally: they are then turned 90° clockwise, so that carbon-1 is on the right. Since such a representation is no longer a true Fischer projection, the vertical bonds should be shown as wedges to avoid any ambiguity:



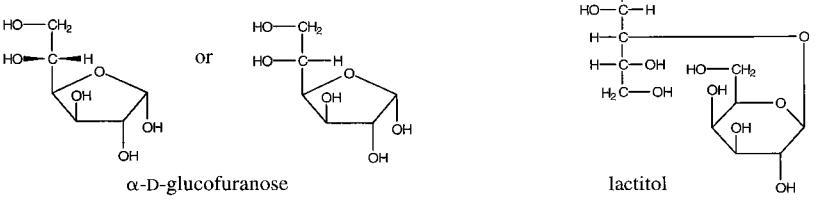
8.2 The Haworth representation is preferably used to show the cyclic forms of monosaccharides, and not those with "chair-shaped" rings. In a pyranose ring, the oxygen is in the upper right-hand corner; in a furanose ring, the oxygen is at the top in the centre. If the configuration of the anomeric carbon is not specified, a wavy line is used. In practice, the conventional Haworth representation is simplified; the lower side of the ring, assumed to be nearer to the observer, is not thickened, and the hydrogen atoms linked to the carbon atoms in the ring are not shown:



conventional simplified α-D-ribofuranose D-idopyranose

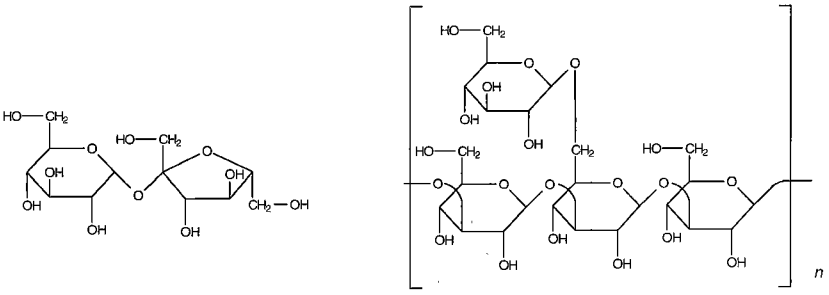
Haworth representation of α-D-glucopyranose

8.3 The non-cyclic part of a saccharide is shown as a Fischer projection (wedges are not necessary):



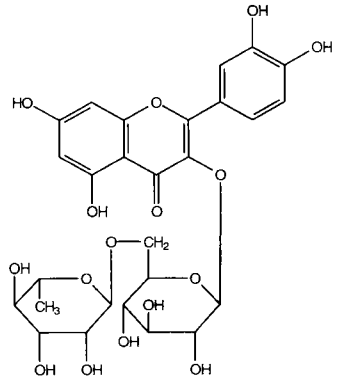
α-D-glucofuranose lactitol

8.4 The standard conventions are used to show the oligo- and polysaccharides:

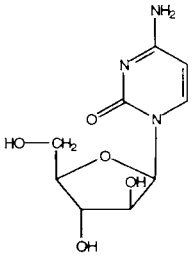


sucrose (saccharose) sizofiran

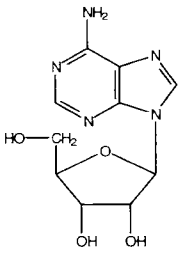
8.5 In structures that are only partly saccharide, that part is shown in accordance with the standard provisions for carbohydrates, and the rest of the structure according to the conventions for acyclic or cyclic chemical compounds, or for compounds such as steroids, polypeptides, etc.:



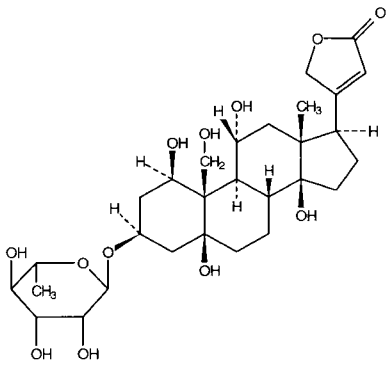
rutoside



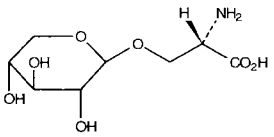
cytarabine



adenosine



ouabain



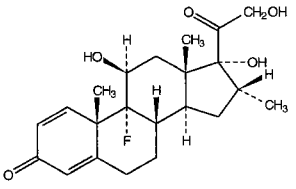
α-xylopyranosyl-L-serine

9. Steroids

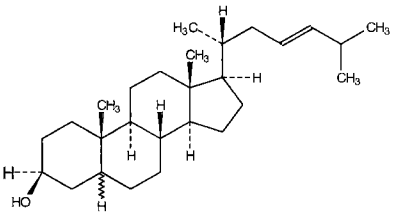
9.1 The rings of a steroid are depicted as a projection on to the plane of the paper. The projection should normally be oriented so that position 3 is at the bottom left and the regular pentagonal ring D at the top right, with position 17 uppermost.

9.2 A bond that lies below the plane of the paper is given the designation α and shown by a broken line; a bond that lies above the plane of the paper is designated as β and shown by a wedge, while a bond whose configuration is not known is designated as ξ and denoted by a wavy line. All the hydrogen atoms attached to centres of asymmetry are shown.

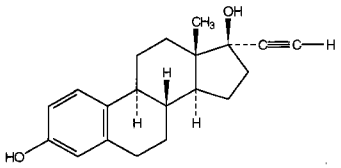
9.3 The backbone of a side-chain at C-17 is best shown as in the plane of the paper (lines of ordinary thickness), the bond between C-17 and C-20 being similarly shown. Side-chains are usually represented by lines at an angle to one another, the terminal groups being set out in full, as shown below. Stereochemistry due to substituents in the chain is indicated by the customary wedges and broken lines:



dexamethasone

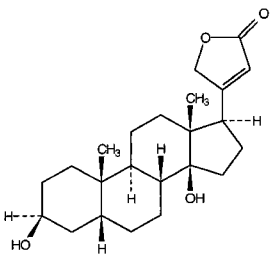


(23*E*)-5ξ-cholest-23-en-3β-ol

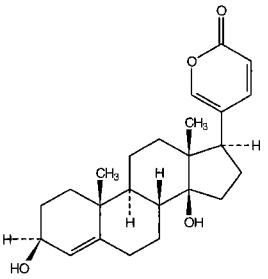


ethinylestradiol

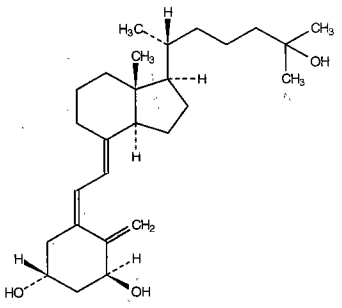
Cardanolides (see also section 8.5), bufanolides and derivatives of calciferol are depicted as shown below:



digitoxigenin



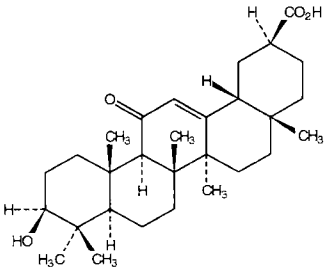
scillarenin



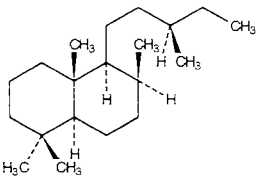
calcitriol

10. Terpenoids

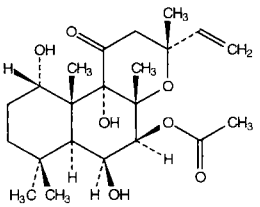
10.1 Terpenes and related compounds are depicted in a similar way to steroids, using the same conventions. Long chains are shown as lines at an angle to one another, all terminal groups being shown in full:



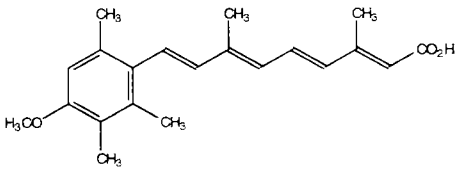
enoxolone



labdane



colforsin

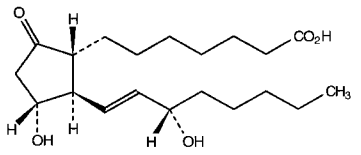


acitretin

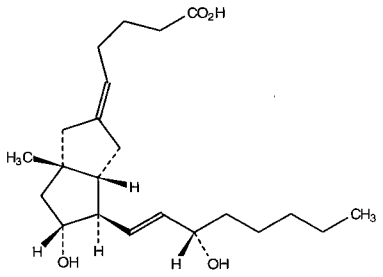
11. Prostanoids

11.1 Prostaglandins and their derivatives are depicted using the same conventions as those applicable to steroids and terpenes. Long chains are

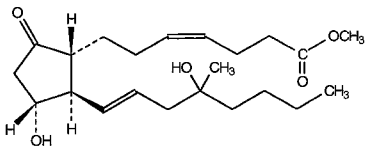
shown as lines at an angle to one another, all terminal groups being shown in full:



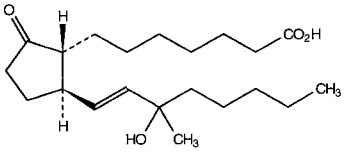
alprostadil



ciprostene

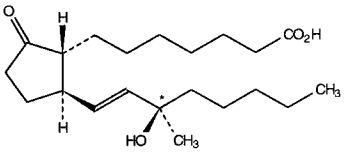


enisoprost



doxaprost

The last two are mixtures of epimers in the carbon chain, which can be shown in the manner indicated in section 7.16:

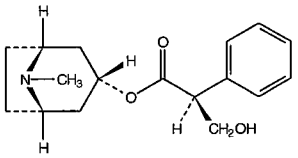


and epimer at C*

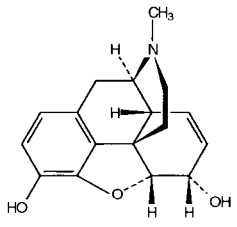
doxaprost

12. Alkaloids

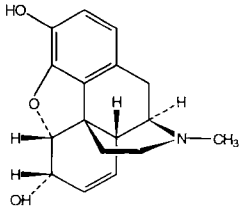
12.1 There are no general rules for depicting alkaloids, though many are depicted with a preferred conventional skeleton that can be used for a family of similar products:



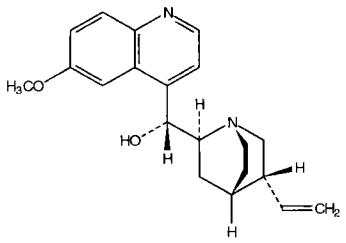
hyoscyamine



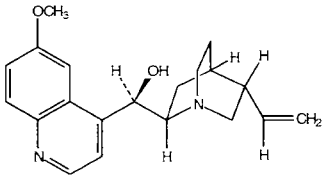
or



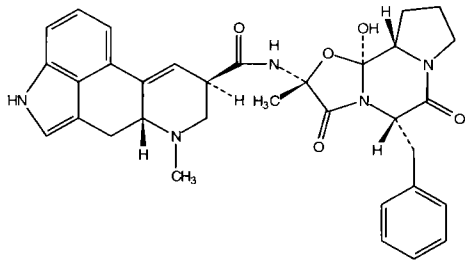
morphine



or



quinine

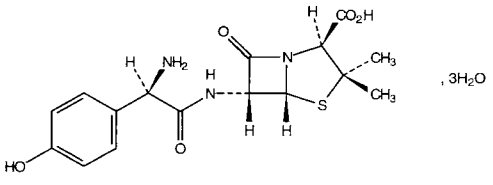


ergotamine

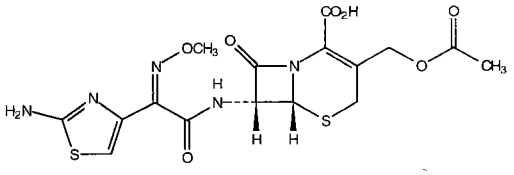
13. Antibiotics

13.1 Some antibiotics can be depicted by means of conventional diagrams that can be used for a family of similar products.

13.2 β-Lactams (penicillins and cefalosporins) are shown as below:

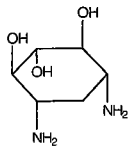


amoxicillin

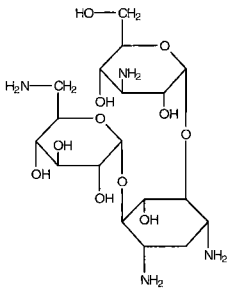


cefotaxime

13.3 Aminosides are related to 2-deoxy-D-streptamine according to the conventions used for carbohydrates:

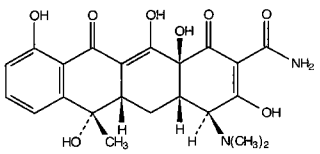


2-deoxy-D-streptamine

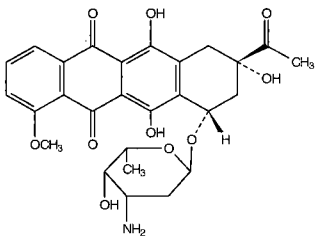


kanamycin

13.4 Tetracyclines and rubicins are depicted as follows:

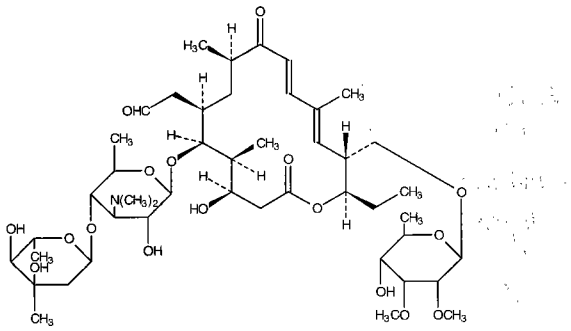


tetracycline

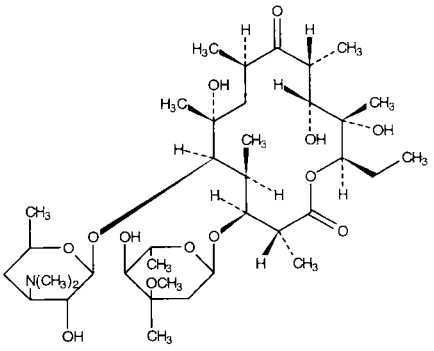


daunorubicin

13.5 The representation of the large rings of macrolides is variable. For example:

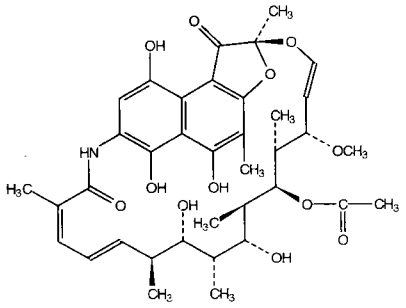


tylosin



erythromycin

13.6 The depiction of derivatives of rifamycin is based on that of the parent structure, which is shown as below:

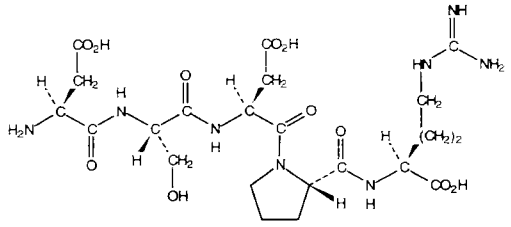


rifamycin

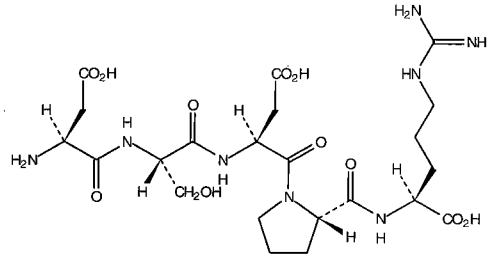
14. Polypeptides

14.1 In polypeptides, the linear sequence of amino acid residues is shown with the amino-terminal residue on the left and the carboxy-terminal residue on the right (followed by "-NH_2" if it is carboxamide).

14.2 Oligopeptides produced by the condensation of fewer than about five amino acids are often depicted in their full form. Since several polypeptides of this type are used as drugs, the full structure may be useful for showing any chemical modifications present:



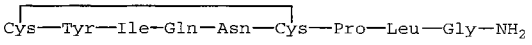
or



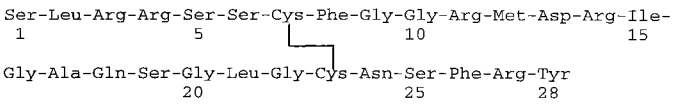
pentigetide

14.3 In the representation of polypeptides, amino acids are shown by means of the standard three-letter codes, peptide bonds being assumed to exist between C-1 and N-2 of adjacent residues. A code given without further qualification means that the amino acid concerned belongs to the L-series. If an amino acid belongs to the D-series, the letter "D" precedes the three-letter code and is joined to it by a hyphen. Unusual residues are shown in full. If a polypeptide occupies more than one line, a hyphen is placed at the end of each successive line until the formula has been completed.

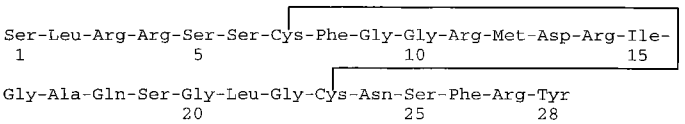
14.4 Disulfide bridges are drawn as lines attaching the S atoms to the "Cys" units but without showing those atoms. The lines must be drawn vertically and appear to pass through the letter "y". They may be placed above or below the unit chain, according to requirements. Either of the forms shown below is acceptable:



oxytocin



or

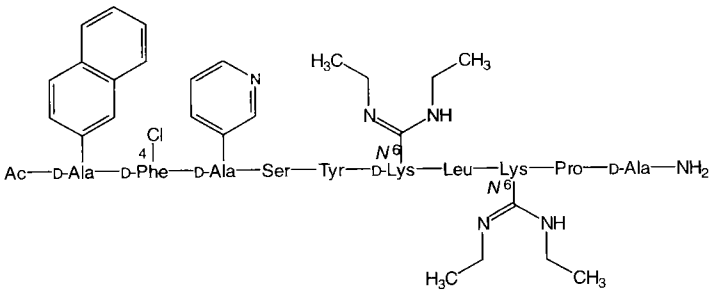


carperitide

Sometimes a mixture of the two styles will be needed so as to ensure that the bridges do not cross over one another.

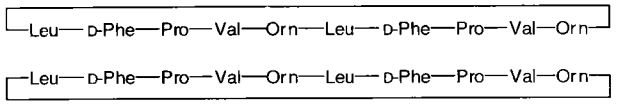
14.5 If an amino acid residue is substituted on the N-2 atom, the symbol for the substituent is placed before the three-letter code. If a side-chain modification occurs, the substituent may be depicted either in full or by

means of its conventional symbol placed above or below the three-letter code and joined to it by a vertical line passing through the central letter. If necessary, a locant is placed beside the vertical line that represents side-chain substitution:

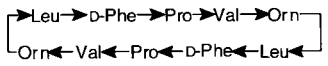


ganirelix

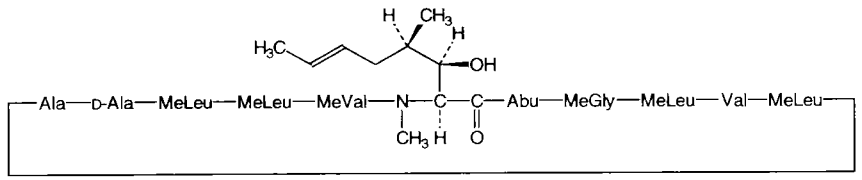
14.6 In cyclic peptides, the amino acid sequence is formulated in the usual manner but the residues at each end of the line are joined by a lengthened bond. If the residues are written on two lines, the sequence is reversed on one of them; hence the CO to NH direction within the peptide bond must be indicated by arrows:



or

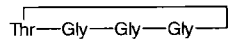


gramicidin S

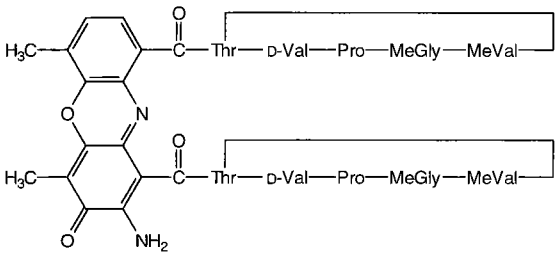


ciclosporin

14.7 Cyclic esters are shown by means of a lengthened bond starting from the carbonyl end of the sequence and ending at the symbol of the hydroxy amino acid:



14.8 If part of the molecule is not polypeptide, it can be represented in accordance with the rules for acyclic or cyclic compounds:



dactinomycin

14.9 In showing polypeptides produced by the condensation of a large number of amino acids, one-letter codes rather than three-letter codes can be used to save space and facilitate computer processing. The one-letter codes are arranged in sets of ten letters separated by a space. For purposes of sequential numbering, the numbers of individual amino acids are generally placed below the codes. As an example, the polypeptide sequence of epoetin alfa:

```
Ala-Pro-Pro-Arg-Leu-Ile-Cys-Asp-Ser-Arg-Val-Leu-Glu-Arg-Tyr-
                                  10
Leu-Leu-Glu-Ala-Lys-Glu-Ala-Glu-Asn-Ile-Thr-Thr-Gly-Cys-Ala-
          20                                            30
Glu-His-Cys-Ser-Leu-Asn-Glu-Asn-Ile-Thr-Val-Pro-Asp-Thr-Lys-
                                  40
Val-Asn-Phe-Tyr-Ala-Trp-Lys-Arg-Met-Glu-Val-Gly-Gln-Gln-Ala-
                    50                                      60
Val-Glu-Val-Trp-Gln-Gly-Leu-Ala-Leu-Leu-Ser-Glu-Ala-Val-Leu-
                                  70
Arg-Gly-Gln-Ala-Leu-Leu-Val-Asn-Ser-Ser-Gln-Pro-Trp-Glu-Pro-
                    80                                      90
Leu-Gln-Leu-His-Val-Asp-Lys-Ala-Val-Ser-Gly-Leu-Arg-Ser-Leu-
                                  100
Thr-Thr-Leu-Leu-Arg-Ala-Leu-Gly-Ala-Gln-Lys-Glu-Ala-Ile-Ser-
          110                                           120
Pro-Pro-Asp-Ala-Ala-Ser-Ala-Ala-Pro-Leu-Arg-Thr-Ile-Thr-Ala-
                                  130
Asp-Thr-Phe-Arg-Lys-Leu-Phe-Arg-Val-Tyr-Ser-Asn-Phe-Leu-Arg-
          140                                           150
Gly-Lys-Leu-Lys-Leu-Tyr-Thr-Gly-Glu-Ala-Cys-Arg-Thr-Gly-Asp
                                  160
```

becomes in abbreviated form:

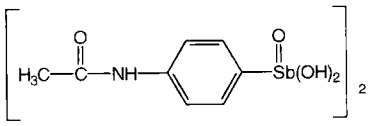
```
APPRLICDSR  VLERYLLEAK  EAENITTGCA  EHCSLNENIT  VPDTKVNPYA

WRKMEVGQQA  VEVWQGLALL  SEAVLRGQAL  LVNSSQPWEP  LQLHVNKAVS

GLRSLTTLLR  ALGAQKEAIS  PPNAASAAPL  RTITADTFRK  LFRVYSNFLR

GKLKLYTGEA  CRTGD
```

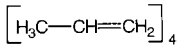
15. Polymers

15.1 The representation of polymers is based on the use of "repeated groups", i.e. sequences of identical groups. These groups are abbreviated $[X]_n$ in square brackets, where n is the number of times that they appear.

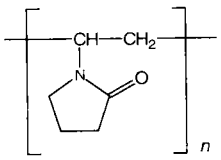
15.2 Repeated groups are either "monomers", i.e. "normal" structural formulae, or "repeated structural units", which are relatively complex multivalent radicals.

15.3 The normal formulae, i.e. those of the relevant monomers, are used when it is difficult to specify how the monomers are bonded, or in order to show simple oligomers with a maximum of eight repeated groups:

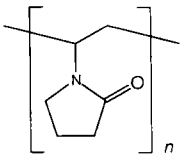




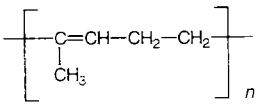
15.4 By and large, polymers are depicted as repeated structural units in which terminal bonds are shown. In linear polymers, such units are bivalent radicals:



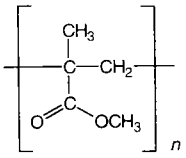
or



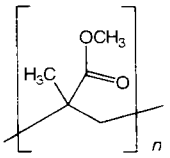
polyvidone



polyisoprene

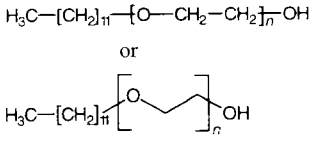


or

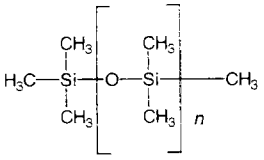


poly(methyl methacrylate)

This also applies to polymers when the terminal groups are shown:

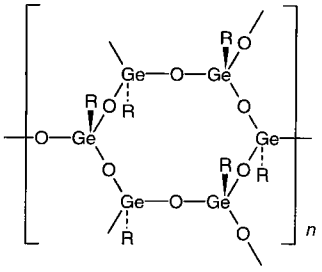


lauromacrogol



dimeticone

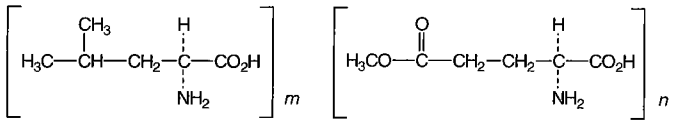
15.5 Network polymers can be shown by multivalent repeated structural units:



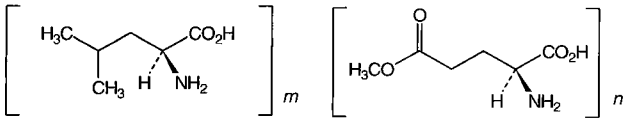
R = —CH_2—CH_2—CO_2H

repagermanium

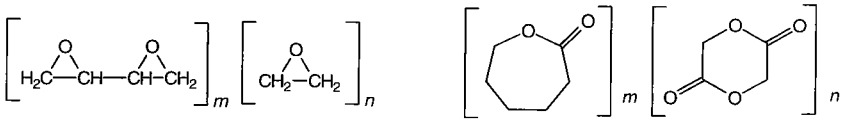
15.6 The representation of copolymers depends on what is known about the bonding of the constituent monomers. Thus normal formulae are used when it is difficult to specify the way in which the monomers are bonded:



or

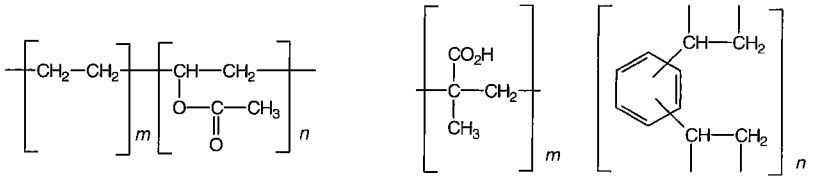


leuciglumer



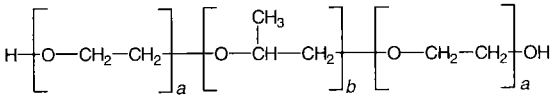
polyetadene poliglecaprone

Repeated structural units are used when the atoms involved in bonding are defined. The bonds are represented as unbroken lines between the monomers when their positions are known, but they are shown as unattached when the way in which the monomers are linked has not been precisely determined:



copolymers of ethene and vinyl ethanoate (acetate) (EVA) polacrilin

15.7 Sequences of polymers are shown in a similar way:



poloxamer

Acknowledgements

Special acknowledgement is made to Professor R.C. Moreau, former President, French Pharmacopoeia Commission, Paris, France, who prepared this Annex, and to Mr R. B. Trigg, Secretary, British Approved Names (BAN) Committee, London, England, for his valuable contribution and assistance in editing it.

References

1. International Union of Pure and Applied Chemistry, Organic Chemistry Division, Commission on the Nomenclature of Organic Chemistry. *Nomenclature of organic chemistry, sections A, B, C, D, E, F, and H,* 4th ed. Oxford, Pergamon, 1979.
2. Leigh GJ, ed. *Nomenclature of inorganic chemistry: recommendations 1990.* Oxford, Blackwell Scientific, 1990.

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Annex 2
List of available International Chemical Reference Substances[1]

International Chemical Reference Substances are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The international pharmacopoeia* or proposed in draft monographs.

Directions for use and the analytical data required for the tests specified in *The international pharmacopoeia* are given in the certificates enclosed with the substances when distributed. More detailed analytical reports on the substances may be obtained on request from the WHO Collaborating Centre for Chemical Reference Substances.

International Chemical Reference Substances may also be used in tests and assays not described in *The international pharmacopoeia.* However, the responsibility for assessing the suitability of the substances then rests with the user or with the pharmacopoeia commission or other authority that has prescribed their use.

It is generally recommended that the substances be stored protected from light and moisture and preferably at a temperature of about +5 °C. When special storage conditions are required, this is stated on the label or in the accompanying leaflet.

The stability of the International Chemical Reference Substances kept at the Collaborating Centre is monitored by regular re-examination, and any materials that have deteriorated are replaced by new batches when necessary. Lists giving control numbers for the current batches are issued in the annual reports from the Centre and may be obtained on request.

Orders for International Chemical Reference Substances should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteksbolaget AB
Centrallaboratoriet
S-105 14 Stockholm
Sweden

Telex: 115 53 APOBOL S
Fax: 46 8 740 60 40

[1] As updated at the thirty-fourth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 28 November–2 December 1994.

International Chemical Reference Substances are supplied only in the standard packages indicated in the following list.

Reference substance	*Package size*
aceclidine salicylate	100 mg
p-acetamidobenzalazine	100 mg
acetazolamide	100 mg
allopurinol	100 mg
2-amino-5-nitrothiazole	25 mg
3-aminopyrazole-4-carboxamide hemisulfate	100 mg
amitriptyline hydrochloride	100 mg
amodiaquine hydrochloride	200 mg
amphotericin B	400 mg
ampicillin (anhydrous)	200 mg
ampicillin sodium	200 mg
ampicillin trihydrate	200 mg
anhydrotetracycline hydrochloride	25 mg
atropine sulfate	100 mg
azathioprine	100 mg
bacitracin zinc	200 mg
beclometasone dipropionate	200 mg
bendazol hydrochloride	100 mg
benzobarbital	100 mg
benzylamine sulfate	100 mg
benzylpenicillin potassium	200 mg
benzylpenicillin sodium	200 mg
bephenium hydroxynaphthoate	100 mg
betamethasone	100 mg
betamethasone valerate	100 mg
betanidine sulfate	100 mg
bupivacaine hydrochloride	100 mg
caffeine	100 mg
carbamazepine	100 mg
carbenicillin monosodium	200 mg
chloramphenicol	200 mg
chloramphenicol palmitate	1 g
chloramphenicol palmitate (polymorph A)	200 mg
5-chloro-2-methylaminobenzophenone	100 mg
2-(4-chloro-3-sulfamoylbenzoyl) benzoic acid	50 mg
chlorphenamine hydrogen maleate	100 mg
chlorpromazine hydrochloride	100 mg
chlortalidone	100 mg
chlortetracycline hydrochloride	200 mg

Reference substance	*Package size*
cimetidine	100 mg
clomifene citrate	100 mg
clomifene citrate *Z*-isomer (*see* zuclomifene)	
cloxacillin sodium	200 mg
colecalciferol (vitamin D_3)	500 mg
cortisone acetate	100 mg
dapsone	100 mg
desoxycortone acetate	100 mg
dexamethasone	100 mg
dexamethasone acetate	100 mg
dexamethasone phosphoric acid	100 mg
dexamethasone sodium phosphate	100 mg
diazepam	100 mg
diazoxide	100 mg
dicloxacillin sodium	200 mg
dicolinium iodide	100 mg
dicoumarol	100 mg
diethylcarbamazine dihydrogen citrate	100 mg
digitoxin	100 mg
digoxin	100 mg
N,N'-di-(2,3-xylyl)anthranilamide	50 mg
dopamine hydrochloride	100 mg
emetine hydrochloride	100 mg
4-epianhydrotetracycline hydrochloride	25 mg
4-epitetracycline hydrochloride	25 mg
ergocalciferol (vitamin D_2)	500 mg
ergometrine hydrogen maleate	50 mg
ergotamine tartrate	50 mg
erythromycin	250 mg
estradiol benzoate	100 mg
estrone	100 mg
etacrynic acid	100 mg
ethambutol hydrochloride	100 mg
ethinylestradiol	100 mg
ethisterone	100 mg
ethosuximide	100 mg
etocarlide	100 mg
flucytosine	100 mg
fluorouracil	100 mg
fluphenazine decanoate dihydrochloride	100 mg
fluphenazine enantate dihydrochloride	100 mg
fluphenazine hydrochloride	100 mg

Reference substance		*Package size*
folic acid		100 mg
3-formylrifamycin		200 mg
framycetin sulfate (neomycin B sulfate)		200 mg
furosemide		100 mg
griseofulvin		200 mg
haloperidol		100 mg
hydrochlorothiazide		100 mg
hydrocortisone		100 mg
hydrocortisone acetate		100 mg
(-)-3-(4-hydroxy-3-methoxyphenyl)-2-hydrazino-2-methylalanine (3-*O*-methylcarbidopa)		25 mg
(-)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine		25 mg
ibuprofen		100 mg
imipramine hydrochloride		100 mg
indometacin		100 mg
o-iodohippuric acid		100 mg
isoniazid		100 mg
lanatoside C		100 mg
levodopa		100 mg
levothyroxine sodium		100 mg
lidocaine		100 mg
lidocaine hydrochloride		100 mg
liothyronine sodium		50 mg
metenamic acid		100 mg
melting point reference substances		
azobenzene	(69 °C)	4 g
vanillin	(83 °C)	4 g
benzil	(96 °C)	4 g
acetanilide	(116 °C)	4 g
phenacetin	(136 °C)	4 g
benzanilide	(165 °C)	4 g
sulfanilamide	(166 °C)	4 g
sulfapyridine	(193 °C)	4 g
dicyanodiamide	(210 °C)	4 g
saccharin	(229 °C)	4 g
caffeine	(237 °C)	4 g
phenolphthalein	(263 °C)	4 g
metazide		100 mg
methaqualone		100 mg
methyldopa		100 mg

Reference substance	*Package size*
methyltestosterone	100 mg
meticillin sodium	200 mg
metronidazole	100 mg
nafcillin sodium	200 mg
neamine hydrochloride (neomycin A hydrochloride)	0.5 mg
neostigmine metilsulfate	100 mg
nicotinamide	100 mg
nicotinic acid	100 mg
niridazole	200 mg
niridazole-chlorethylcarboxamide	25 mg
norethisterone	100 mg
norethisterone acetate	100 mg
nystatin	200 mg
ouabain	100 mg
oxacillin sodium	200 mg
oxytetracycline dihydrate	200 mg
oxytetracycline hydrochloride	200 mg
papaverine hydrochloride	100 mg
pheneticillin potassium	200 mg
phenoxymethylpenicillin	200 mg
phenoxymethylpenicillin calcium	200 mg
phenoxymethylpenicillin potassium	200 mg
phenytoin	100 mg
prednisolone	100 mg
prednisolone acetate	100 mg
prednisone	100 mg
prednisone acetate	100 mg
probenecid	100 mg
procaine hydrochloride	100 mg
procarbazine hydrochloride	100 mg
progesterone	100 mg
propicillin potassium	200 mg
propranolol hydrochloride	100 mg
propylthiouracil	100 mg
pyrantel embonate	500 mg
pyridostigmine bromide	100 mg
reserpine	100 mg
retinol acetate (solution)	5 capsules[1]
riboflavin	250 mg

[1] Each containing about 9 mg in 250 mg of oil.

Reference substance	*Package size*
rifampicin	200 mg
rifampicin quinone	200 mg
sodium cromoglicate	100 mg
spectinomycin hydrochloride	200 mg
sulfamethoxazole	100 mg
sulfamethoxypyridazine	100 mg
sulfanilamide	100 mg
sulfasalazine	100 mg
testosterone propionate	100 mg
tetracycline hydrochloride	200 mg
thioacetazone	100 mg
4,4′-thiodianiline	50 mg
L-thyroxine sodium *see* levothyroxine sodium	
tolbutamide	100 mg
tolnaftate	100 mg
trimethadione	200 mg
trimethoprim	100 mg
trimethylguanidine sulfate	100 mg
tubocurarine chloride	100 mg
vitamin A acetate (solution) *see* retinol acetate (solution)	
vincristine sulfate	9.7 mg/vial
warfarin	100 mg
zuclomifene	50 mg

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Annex 3
List of available International Infrared Reference Spectra

International Infrared Reference Spectra are established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Full-scale reproductions of spectra produced from authenticated material on a suitable instrument are supplied for use in identification tests described in the specifications for quality control of drugs published in *The international pharmacopoeia* or proposed in draft monographs.

Precise instructions for the preparation of spectra are given on the label of each reference spectrum. All International Infrared Reference Spectra are distributed together with a document giving further details on the use of such spectra, entitled "General recommendations for the preparation and use of infrared spectra in pharmaceutical analysis" (see Annex 4).

Orders for International Infrared Reference Spectra should be sent to:

WHO Collaborating Centre for Chemical Reference Substances
Apoteksbolaget AB
Centrallaboratoriet
S-105 14 Stockholm
Sweden

Telex: 115 53 APOBOL S
Fax: 46 8 740 60 40

The following International Infrared Reference Spectra are currently available from the Centre:[1]

aceclidine salicylate
acetazolamide
allopurinol
amitriptyline hydrochloride
ampicillin trihydrate

benzylpenicillin potassium
biperiden
biperiden hydrochloride
bupivacaine hydrochloride

[1] Spectra for several other substances are still being validated and are not yet available for distribution.

caffeine (anhydrous)
chlorphenamine hydrogen maleate
clofazimine
cloxacillin sodium
colchicine
cytarabine

dextromethorphan hydrobromide
diazepam
dicolinium iodide
dicoumarol
diethylcarbamazine dihydrogen citrate
diphenoxylate hydrochloride

erythromycin ethylsuccinate
erythromycin stearate
etacrynic acid
ethionamide
ethosuximide

furosemide

gallamine triethiodide
glibenclamide

haloperidol
hydrochlorothiazide

ibuprofen
imipramine hydrochloride
indometacin
isoniazid

lidocaine
lidocaine hydrochloride
lindane

metronidazole
miconazole nitrate

niclosamide
nicotinamide
noscapine

oxamniquine

papaverine hydrochloride
phenobarbital

phenoxymethylpenicillin calcium
phenytoin
primaquine phosphate
propylthiouracil
protionamide
pyrimethamine

salbutamol
salbutamol sulfate
sulfadimidine
sulfadoxine
sulfamethoxazole
sulfamethoxypyridazine

tiabendazole
trihexyphenidyl hydrochloride
trimethoprim

verapamil hydrochloride

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Annex 4
General recommendations for the preparation and use of infrared spectra in pharmaceutical analysis

1. Introduction

In pharmaceutical analysis the region of the electromagnetic spectrum used is 4000-600 cm^{-1} (wavelength 2.5-16.7 μm), i.e. the mid-infrared. Spectrophotometric measurements in this region are mainly used for identification purposes. Except for enantiomers, which have identical spectra in solution, the infrared spectrum of any given substance is unique. Polymorphism and other factors, such as variations in crystal size and orientation, the grinding procedure, and the possible formation of hydrates may, however, be responsible for minor, and occasionally substantial, variations in the infrared spectrum of a substance in the solid state. The infrared spectrum is not usually greatly affected by the presence of small quantities of impurities in the substance tested. For identification purposes, the spectrum may be compared with that of a reference substance, concomitantly prepared, or with a reference spectrum.

The terms *absorbance, transmittance, absorptivity* and *absorption spectrum* are defined in *The international pharmacopoeia,* 3rd ed., Vol. 1, pp. 33-34, in the chapter "Spectrophotometry in the visible and ultraviolet regions".

2. Apparatus

Conventional infrared spectrometers disperse the infrared radiation by means of either gratings or prisms. The development of computerized laboratory equipment provides the additional option of using an interferometer coupled to a computer for the reduction of the data, by performing a Fourier transformation of the interferogram, to generate an infrared spectrum. These instruments are called Fourier transform infrared spectrometers (FTIRs). Apart from small differences in the low-frequency cut-off, all of the above types of infrared instruments generate comparable data and can generally be used interchangeably for qualitative analyses. However, each instrument will possess specific signal-to-noise and resolution characteristics.

Spectrophotometers suitable for use for identification tests should normally operate in the range 4000-600 cm^{-1} (2.5-16.7 μm) or in some cases up to 250 cm^{-1} (40 μm). If the attenuated total reflectance technique

is to be used, the instrument must be equipped with a suitable attachment consisting of a single or multireflecting element. The attachment and a suitable mounting should permit its alignment in the spectrophotometer for maximum transmission.

3. Method of verification of frequency scale and resolution

The spectrum of a polystyrene film of suitable thickness, normally between 0.03 mm and 0.05 mm, is recorded. This includes maxima at the following frequencies, expressed as wavenumbers in cm^{-1}: 3027, 2851, 2924, 1944, 1871, 1802, 1601, 1583, 1181, 1154, 1069, 1028, 907, 699. Acceptable tolerances are ± 8 cm^{-1} for the range 4000-2000 cm^{-1} and ± 4 cm^{-1} for the range 2000-600 cm^{-1}.

The difference between the percentage transmittance of the absorption minimum at 2870 cm^{-1} and that of the absorption maximum at 2851 cm^{-1} should be greater than 18 and the difference between the percentage transmittance of the absorption minimum at 1589 cm^{-1} and that of the absorption maximum at 1583 cm^{-1} should be greater than 12.

4. Environment

Precautions should be taken to minimize exposure to atmospheric moisture during sample preparation. It is advisable to store the halide salts, the sodium chloride or other similar plates, and all necessary accessories in a desiccator at room temperature over silica gel, and to prepare the samples in an area of controlled temperature and humidity; alternatively, all manipulations should be carried out under an infrared lamp.

5. Use of solvents

The solvent used in infrared spectrophotometry must not affect the cell, which usually consists of a halide salt such as sodium chloride or potassium bromide. Where possible, spectral grade solvents should be used.

No solvent is completely transparent throughout the entire infrared spectrum. Carbon tetrachloride R[1] is practically transparent (up to 1 mm of thickness) over the range 4000-1700 cm^{-1} (2.5-5.9 µm). Dichloromethane R and dibromomethane R are useful solvents. Carbon disulfide IR[2] (up to 1 mm in thickness) is suitable as a solvent up to 250 cm^{-1} (40 µm) except in the 2400-2000 cm^{-1} (4.2-5 µm) and the 1800-1300 cm^{-1} (5.6-7.7 µm) regions, where it has strong absorption. Its weak absorption in the 875-845 cm^{-1} (11.4-11.8 µm) region should be noted. Other solvents have relatively narrow regions of transparency.

[1] R: of reagent-grade quality.
[2] IR: of suitable purity for use in spectrophotometry in the infrared region.

6. Preparation of the substance to be examined

To obtain a suitable infrared absorption spectrum, it is necessary to follow the instructions given below for the preparation of the substance. Substances in liquid form may be tested directly or in a suitable solution. The usual methods of preparation for solid substances include dispersing the finely ground solid specimen in mineral oil, incorporating it in a transparent disc or pellet obtained by mixing it thoroughly with previously dried potassium halide and compressing the mixture in a die, or preparing a solution in a suitable solvent. Preparation of the substance for the attenuated total reflectance technique is described separately.

6.1 *Method 1*

The solid substance should be triturated with dry, finely powdered potassium halide (normally potassium bromide). When hydrochlorides are being examined, potassium chloride should be employed to avoid the risk of halide exchange.

The ratio of substance to halide salt should be about 1 to 200-300, e.g. 1.5 mg in 300 mg of the halide salt in the case of prism instruments, or about 1.0 mg in 300 mg of the halide salt for grating or Fourier transform instruments. The mixture should be carefully ground by means of an agate mortar and pestle for 1 minute. In exceptional cases, the use of a ball mill may be indicated, but the resulting risk of producing polymorphic changes generally outweighs any improvement in resolution. The triturate should then be uniformly spread in a suitable die and compressed, under vacuum, at a pressure of about 800 MPa. As an alternative, potassium halide discs can be prepared by means of a hand-held minipress. The disc thus produced is mounted in a suitable holder.

Several factors, e.g. inadequate or excessive grinding or moisture or other impurities in the halide carrier, may give rise to unsatisfactory discs. Unless its preparation presents particular difficulties, a disc should be rejected if visual inspection shows lack of uniformity or if the transmittance at about 2000 cm^{-1} (5 μm), in the absence of a specific absorption band, is less than 75% without compensation.

The quality of a spectrum is often improved by placing a blank disc of the appropriate potassium halide, of similar thickness to that of the sample disc, in the reference beam.

6.2 *Method 2*

A small quantity of the finely ground substance should be triturated with the minimum amount of a suitable mineral oil (e.g. Nujol) or other suitable liquid to give a smooth creamy paste; 10 mg of the substance to be examined combined with 1-2 drops of mineral oil is often sufficient to prepare a satisfactory mull. The prepared mull should appear opaque.

A portion of the mull is then compressed between two flat sodium chloride or other suitable halide-salt plates.

If the spectrum of the mineral oil used interferes with regions of interest, an additional dispersion of the substance in a medium such as a suitable fluorinated hydrocarbon oil or hexachlorobutadiene R is prepared, and the spectrum recorded in those regions where the mineral oil shows strong absorption.

6.3 ***Method 3***

A capillary film of the liquid held between two sodium chloride plates or a filled cell of suitable thickness is used.

6.4 ***Method 4***

A solution in a suitable solvent is prepared and a concentration and cell thickness are chosen to give a satisfactory spectrum over a sufficiently wide wave number range. Generally, good spectra are obtained with concentrations of 1-10% w/v for a cell thickness of 0.1-0.5 mm. To compensate for the absorption of the solvent, a cell of matched path-length containing the solvent used is placed in the reference beam or a spectrum of the solvent is obtained so as to permit differentiation between solvent and sample absorptions. Alternatively, the solvent absorbance spectrum versus air may be subtracted from the solution spectrum versus air to obtain the absorbance spectrum of the solute. (When an FTIR instrument is used, the spectrum of the solvent recorded under identical conditions can be subtracted digitally.)

6.5 ***Method 5***

Gases are examined in a cell with windows transparent to infrared radiation and having an optical path-length of about 100 mm. The cell is evacuated and filled to the desired pressure through a stopcock or needle valve by means of a suitable gas-transfer line between the cell and the container of the substance to be examined. If necessary, the pressure in the cell is adjusted to atmospheric pressure with a gas transparent to infrared radiation (e.g. nitrogen R or argon R). To avoid absorption interferences due to water, carbon dioxide or other atmospheric gases, an identical cell that is either evacuated or filled with the gas transparent to infrared radiation is placed in the reference beam.

7. Identification by reference substance

Both the substance to be examined and the reference substance are prepared by means of the same method and the spectrum of each from about 4000 to 600 cm^{-1} (2.5-16.7 μm) is recorded. The concentration of the substance should be such that the strongest peak attributable to it corresponds to a transmittance of about 10%.

If the positions and relative intensities of the absorbance maxima in the spectrum of the substance to be examined are not concordant with those of the spectrum of the reference substance when spectra are obtained by methods 1 or 2, this may be the consequence of differences in crystalline form. To avoid this difficulty, one of the procedures described below may be used for both the substance to be examined and the reference substance:

- Solutions of the reference substance and of the sample, of a suitable concentration, are prepared as described in method 4.
- A small amount (2 or 3 drops) of a concentrated solution in a volatile organic solvent is placed on a blank disc of potassium halide and evaporated to dryness in an oven at 105 °C.
- A small amount (2 or 3 drops) of concentrated solution in a volatile organic solvent is mixed with 300 mg of potassium halide and evaporated to dryness in an oven at 105 °C. Both the reference substance and the substance to be examined are treated in the same manner and then prepared as described in method 1.
- Both the reference substance and the substance to be examined are recrystallized from a suitable solvent.

8. Identification by reference spectrum

The substance to be examined is prepared exactly as described in the note accompanying the International Infrared Reference Spectrum and the spectrum from about 4000 to 600 cm^{-1} (2.5-16.7 μm) recorded by means of an instrument that is checked frequently to ensure that it meets the standards of performance required. The reference maxima of a polystyrene film should be superimposed on the spectrum of the substance to be examined at about 2851 cm^{-1} (3.5 μm), 1601 cm^{-1} (6.25 μm) and 1028 cm^{-1} (9.73 μm). Other suitable polystyrene bands can be superimposed if interference occurs with the bands of the substance. If these polystyrene maxima are taken into account, the identification is considered to be positive if the principal absorbance maxima in the spectrum of the substance to be examined are concordant with the corresponding maxima in the relevant International Infrared Reference Spectrum. When the two spectra are compared, care should be taken to allow for the possibility of differences in resolving power between the instrument on which the International Infrared Reference Spectrum was prepared and that being used to examine the substance. An International Infrared Reference Spectrum of polystyrene recorded on the same instrument as the collection of the reference spectra should be used for assessing these differences. The greatest variation due to differences in resolving power is likely to occur in the region between 4000 and 2000 cm^{-1} (2.5 and 5 μm). However, if the positions and relative intensities of the absorbance maxima in the spectrum of the substance to be examined are not concordant with those of the reference spectrum when methods 1 or 2 are used, this may be due to differences in crystalline form. Another

procedure, as described in section 7, will then be indicated in the note accompanying the reference spectrum.

9. Reflectance techniques

9.1 *Attenuated total reflectance technique*

The attenuated total reflectance (ATR) technique is best adapted to smooth, flexible surfaces, such as various plastics, or to strongly absorbing liquids and solutions, but can also be employed to determine the infrared absorption spectra of solid substances. It is usually necessary to reduce the solid substance to a fine powder, which is then packed directly against the reflecting element of the attachment. Alternatively, an adhesive tape can be used to facilitate the contact, the powdered substance being spread on the adhesive side of the tape to form an almost translucent layer, after which the powdered side of the tape is pressed on to the reflecting element. The backing plate is then attached, or moderate pressure applied by means of a suitable clamp for 1-2 minutes. Finally, the reflecting element is placed in the holder. The tape used in the procedure should preferably contain a natural rubber adhesive. Some plastic materials may be placed directly on to the reflecting element.

Reflective elements are usually made of zinc selenide (refractive index = 2.3) or germanium (refractive index = 4.0). The correct alignment of the attachment in the apparatus should be carefully checked.

9.2 *Diffuse reflectance*

In this technique, the surface of a sample reflects light in many different directions. The solid substance is reduced to a fine powder with a non-absorbing matrix (potassium bromide or chloride is suitable for this purpose). The mixture is placed directly in the sample cup holder of the diffuse reflectance instrument. The spectrum of the matrix recorded under identical conditions should be subtracted digitally. Some plastic materials can be placed directly in the sample cup holder of the diffuse reflectance accessory.

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Annex 5
Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms

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 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.

[1] "Shelf-life specification" means the requirements to be met throughout the shelf-life of the drug product (should not be confused with "release specification").

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.

1.2 *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 of stability) formulations and container-closure systems	Accelerated	Development of the 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, 119:321-324.)

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 1 month at 20 °C and 1 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. *Drug 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. 67).
[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 II – 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 15 °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;[1]
– store between 2 and 8 °C (under refrigeration, no freezing);
– store below 8 °C (under refrigeration);
– store between –5 and –20 °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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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	box ☐	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 pharmacopoeial test(s)

Organoleptic
1. change of colour ☐
2. visible changes, i.e. capping. cracking, foam ☐

Microbial
1. microorganisms visible ☐
2. tests for bacteria positive ☐

Organoleptic (continued)

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 (continued)

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	methyldopa
aminophylline	
ampicillin	nifedipine
benzylpenicillin	paracetamol
	phenoxymethylpenicillin
chloramphenicol	propranolol
chloroquine	
chlorpromazine	spironolactone
	sulfamethoxazole + trimethoprim
epinephrine	suxamethonium bromide
ergometrine	
ethinylestradiol	tetracycline
	thiamine
glyceryl trinitrate	
	warfarin
ibuprofen	
indometacin	
isosorbide dinitrate	

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 von 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..

WHO Technical Report Series, No. 863, 1996

Annex 6
Good manufacturing practices: guidelines on the validation of manufacturing processes

Introduction

These guidelines do not constitute additional requirements in the area of good manufacturing practices (GMP). The purpose of this Annex is to explain and promote the concept of validation, and to assist in establishing priorities and selecting approaches when a validation programme is being developed. Since the WHO guide on GMP (*1*) is applicable essentially to the manufacture of pharmaceutical dosage forms, this text is also concerned with the production of such finished forms. However, the general principles of process validation outlined here are relevant mainly to the manufacture of active ingredients. While the emphasis is on the production processes, many recommendations are also valid for supporting operations, such as cleaning. Analytical validation is not discussed here.[1] Further advice is given in "Validation of analytical procedures used in the examination of pharmaceutical materials" (*2*).

[1] Analytical validation seeks to demonstrate that the analytical methods yield results which permit an objective evaluation of the quality of the pharmaceutical product as specified. The person responsible for the quality control laboratory should ensure that test methods are validated. The analytical devices used for these tests should be qualified and the measuring instruments used for the qualification should be calibrated. Each new test procedure should be validated.

The guide on GMP for pharmaceutical products (section 5) (*1*, page 27) requires the validation of critical processes as well as of changes in the manufacturing process which may affect product quality. Experience shows that few manufacturing processes do not contain steps which are "critical" that may cause variations in final product quality. A prudent manufacturer would therefore normally validate all production processes and supporting activities, including cleaning operations. The term "critical process" in this context indicates a process, operation or step that requires particularly close attention, e.g. sterilization, where the effect on product quality is crucial. It may be noted that certain GMP guides, e.g. that of the European Community (*3*), do not distinguish between critical and non-critical processes from the point of view of validation.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

calibration
The performance of tests and retests to ensure that measuring equipment (e.g. for temperature, weight, pH) used in a manufacturing process or analytical procedure (in production or quality control) gives measurements that are correct within established limits.

certification
The final review and formal approval of a validation or revalidation, followed by approval of a process for routine use.

challenge tests/worst case
A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, that pose the greatest chance of process or product failure when compared with ideal conditions.

installation qualification
The performance of tests to ensure that the installations (such as machines, measuring devices, utilities, manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

manufacturing process[1]
The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

[1] For the purpose of this Annex, "manufacturing process" is used as a synonym of "production process".

operational qualification
Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

qualification of equipment
The act of planning, carrying out and recording the results of tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.

revalidation
Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

validation
The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes – including equipment, buildings, personnel and materials – are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do. Other definitions also exist, e.g. that given in the guidelines on GMP for pharmaceutical products (*1,* page 22).

validation protocol (or plan)
A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process – or a part thereof – for routine use.

validation report
A document in which the records, results and evaluation of a completed validation programme are assembled. It may also contain proposals for the improvement of processes and/or equipment.

General

Validation is an integral part of quality assurance, but the use of this term in connection with manufacturing often gives rise to difficulties. As defined above, it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated operation is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications, and has therefore been formally approved.

Unlike many other requirements of GMP, validation in itself does not improve processes. It can only confirm (or not, as the case may be) that the process has been properly developed and is under control. Ideally, any development activity in the later stages should be finalized by

a validation phase.[1] This includes, in particular, the manufacture of investigational products and the scaling up of processes from pilot plant to production unit. In this event, GMP as *manufacturing* practice may only be concerned with revalidation, e.g. when processes are transferred from development to production, after modifications are introduced (in starting materials, equipment, etc.) or when periodic revalidation is performed.

However, it cannot be assumed that all processes in the pharmaceutical industry worldwide have been properly validated at the development stage. Consequently, validation is discussed here in a broader context as an activity which is initiated in development and is continued until the stage of full-scale production is reached. In fact, it is in the course of development that critical processes, steps or unit operations are identified.

Good validation practice requires the close collaboration of departments such as those concerned with development, production, engineering, quality assurance and control. This is most important when processes go into routine full-scale production following pharmaceutical development and pilot-plant operations. With a view to facilitating subsequent validation and its assessment in the course of quality audits or regulatory inspections, it is recommended that all documentation reflecting such transfers be kept together in a separate file ("technology transfer document").

Adequate validation may be beneficial for the manufacturer in many ways:

- It deepens the understanding of processes, decreases the risks of processing problems, and thus assures the smooth running of the process.
- It decreases the risks of defect costs.
- It decreases the risks of regulatory non-compliance.
- A fully validated process may require less in-process control and end-product testing.

1. Types of process validation

Depending on when it is performed in relation to production, validation can be prospective, concurrent, retrospective or revalidation (repeated validation).

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps: these are then evaluated on the basis of past experience to determine whether they might lead to critical situations.

[1] It may be noted that in some countries data on process validation are required at the preregistration stage (in the submission of, or application for, marketing authorizations).

Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the production scale, e.g. in the preparation of injectable products.

Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. *The first three production-scale batches must be monitored as comprehensively as possible.*[1] The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring.

Concurrent validation together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

Retrospective validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analysed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.

Retrospective validation is obviously not a quality assurance measure in itself, and should never be applied to new processes or products. It may be considered in special circumstances only, e.g. when validation requirements are first introduced in a company. Retrospective validation may then be useful in establishing the priorities for the validation programme. If the results of a retrospective validation are positive, this indicates that the process is not in need of immediate attention and may be validated in accordance with the normal schedule. For tablets which have been compressed under individual pressure-sensitive cells, and with qualified equipment, retrospective validation is the most comprehensive test of the overall manufacturing process of this dosage form. On the other hand, it should not be applied in the manufacture of sterile products.

Revalidation is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality.

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[1] This careful monitoring of the first three production batches is sometimes regarded as prospective validation.

Revalidation may be divided into two broad categories:

- Revalidation after any change having a bearing on product quality.
- Periodic revalidation carried out at scheduled intervals.

Revalidation after changes. Revalidation must be performed on introduction of any changes affecting a manufacturing and/or standard procedure having a bearing on the established product performance characteristics. Such changes may include those in starting material, packaging material, manufacturing processes, equipment, in-process controls, manufacturing areas, or support systems (water, steam, etc.). Every such change requested should be reviewed by a qualified validation group, which will decide whether it is significant enough to justify revalidation and, if so, its extent.

Revalidation after changes may be based on the performance of the same tests and activities as those used during the original validation, including tests on subprocesses and on the equipment concerned. Some typical changes which require revalidation include the following:

- Changes in the starting material(s). Changes in the physical properties, such as density, viscosity, particle size distribution, and crystal type and modification, of the active ingredients or excipients may affect the mechanical properties of the material; as a consequence, they may adversely affect the process or the product.
- Changes in the packaging material, e.g. replacing plastics by glass, may require changes in the packaging procedure and therefore affect product stability.
- Changes in the process, e.g. changes in mixing time, drying temperature and cooling regime, may affect subsequent process steps and product quality.
- Changes in equipment, including measuring instruments, may affect both the process and the product; repair and maintenance work, such as the replacement of major equipment components, may affect the process.
- Changes in the production area and support system, e.g. the rearrangement of manufacturing areas and/or support systems, may result in changes in the process. The repair and maintenance of support systems, such as ventilation, may change the environmental conditions and, as a consequence, revalidation/requalification may be necessary, mainly in the manufacture of sterile products.
- Unexpected changes and deviations may be observed during self-inspection or audit, or during the continuous trend analysis of process data.

Periodic revalidation. It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wear may also cause gradual changes. Consequently, revalidation at scheduled times is advisable even if no changes have been deliberately made.

The decision to introduce periodic revalidation should be based essentially on a review of historical data, i.e. data generated during in-process and finished product testing after the latest validation, aimed at verifying that the process is under control. During the review of such historical data, any trend in the data collected should be evaluated.

In some processes, such as sterilization, additional process testing is required to complement the historical data. The degree of testing required will be apparent from the original validation.

Additionally, the following points should be checked at the time of a scheduled revalidation:

- Have any changes in master formula and methods, batch size, etc., occurred? If so, has their impact on the product been assessed?
- Have calibrations been made in accordance with the established programme and time schedule?
- Has preventive maintenance been performed in accordance with the programme and time schedule?
- Have the standard operating procedures (SOPs) been properly updated?
- Have the SOPs been implemented?
- Have the cleaning and hygiene programmes been carried out?
- Have any changes been made in the analytical control methods?

2. Prerequisites for process validation

Before process validation can be started, manufacturing equipment and control instruments, as well as the formulation, must be qualified. The formulation of a pharmaceutical product should be studied in detail and qualified at the development stage, i.e. before the application for the marketing authorization is submitted. This involves preformulation studies, studies on the compatibility of active ingredients and excipients, and of final drug product and packaging material, stability studies, etc.

Other aspects of manufacture must be validated, including critical services (water, air, nitrogen, power supply, etc.), and supporting operations, such as equipment cleaning and sanitation of premises. Proper training and motivation of personnel are prerequisites to successful validation.

3. Approaches

Two basic approaches to the validation of the process itself exist (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors, etc.), namely the experimental approach and the approach based on the analysis of historical data.

The experimental approach, which is applicable to both prospective and concurrent validation, may involve:

- Extensive product testing.
- Simulation process trials.
- Challenge/worst case trials.
- Controls of process parameters (mostly physical).

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution, and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, subvisual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

Simulation process trials are used mainly to validate the aseptic filling of parenteral products that cannot be terminally sterilized. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. In the past, a level of contamination of less than 0.3% was considered to be acceptable; however, the current target level should not exceed 0.1%.

Challenge experiments are performed to determine the robustness of the process, i.e. its capacity to operate smoothly when parameters approach acceptable limits. The use of ranges of parameters for the quality of the starting materials in experimental batches may make it possible to estimate the extent to which the process is still capable of producing an end-product that meets the specifications.

The physical parameters of the process are monitored in normal production runs to obtain additional information on the process and its reliability. Extra temperature-sensitive devices installed in an autoclave or dry-heat sterilizer (in addition to probes used routinely) will permit an in-depth study of the heat distribution for several loads. Heat-penetration measurements are recommended for injectable products of higher viscosity or with volumes larger than 5 ml. A tableting press equipped

with pressure-sensitive cells will be helpful in collecting statistical data on the uniformity of die-fill and therefore on mass uniformity.

In the approach based on the analysis of historical data, no experiments are performed in retrospective validation, but instead all available historical data concerning a number of batches are combined and jointly analysed. If production is proceeding smoothly during the period preceding validation, the data from in-process inspection and final testing of the product are combined and treated statistically. The results, including the outcome of process capability studies, trend analysis, etc., will indicate whether the process is under control or not.

Quality control charts may be used for retrospective validation. A total of 10–25 batches or more are used for this purpose, preferably processed over a period of no longer than 12 months, and reviewed together. (Batches rejected during routine quality control are not included in this review since they belong to a different "population", but failure investigations are performed separately.) A critical quality parameter of the end-product is selected, e.g. the assay value or potency, unit dose uniformity, disintegration time, or extent of dissolution. The analytical results for this parameter for the batches under review are extracted from past batch release documentation and pooled together, while the results from each batch are treated as subgroups. The grand average ("process average") and control limits are calculated and plotted on graphs or charts in accordance with the instructions given in numerous publications on control charts (see Bibliography, page 91).

A careful review of the charts will enable the reliability of the process to be estimated. A process may be considered reliable if the plotted data are within the control limits and the variability of individual results is stable or tends to decrease. Otherwise, an investigation and possibly an improvement are needed.[1]

In addition, information on product-related problems is also analysed. The reliability of the process is demonstrated if, for a considerable time, there are no rejections, complaints, returns, unaccountable adverse reactions, etc. The process may be certified as retrospectively validated if the results of statistical analysis are positive and the absence of serious problems is documented. However, it should be emphasized that this approach is not applicable to the manufacture of sterile products.

[1] It may be noted that, once control charts for past batches have been prepared, they become a powerful tool for prospective quality management. Data for new batches are plotted on the same charts and, for every result outside control limits, a reason, that is a new factor affecting the process, is sought and, when found, eliminated. By consistently applying this approach over a period of time the process may be considerably improved.

Table 1
Example of priorities for a process validation programme

Type of process	Validation requirements
New	Every new process must be validated before approval for routine production
Existing:	
Processes designed to render a product sterile	All processes affecting sterility and manufacturing environment must be validated; the most important is the sterilization stage
Non-sterile production	Low-dose tablets and capsules containing highly active substances: validation of mixing and granulation in relation to content uniformity
	Other tablets and capsules: validation of tablet compressing and capsule filling in relation to uniformity of mass

4. Organization

Several possible methods of organizing validation are available, one of which is the establishment of a validation group. For this purpose, the management appoints a person responsible for validation (validation officer), who then forms the group (team, committee). This is headed by a group leader, and represents all major departments: development, production, engineering, quality assurance and control. The composition of the group should be changed from time to time to give opportunities to other people to generate new ideas and to gain experience. The validation group then prepares a programme, which determines the scope of its work, its priorities, the time-schedule, the resources needed, etc. The programme is sent for review and approval to the departments and functions concerned. The final review and approval are the responsibility of the validation officer.

5. Scope of a process validation programme

Suggested priorities for a validation programme are listed in Table 1. For new processes, it is recommended that the first few full-scale production batches (e.g. three batches) should not be released from quarantine after approval by the quality control department until the validation has been completed, the results presented and reviewed, and the process approved (certified).

6. Validation protocol and report

A suggested scheme for the validation protocol and subsequent report concerning a particular process is shown below:

Part 1. Purpose (the validation) and prerequisites

Part 2. Presentation of the entire process and subprocesses, flow diagram, critical steps/risks

Part 3. Validation protocol, approval

Part 4. Installation qualification, drawings

Part 5. Qualification protocol/report

5.1 Subprocess 1

5.1.1 Purpose

5.1.2 Methods/procedures, list of manufacturing methods, SOPs, and written procedures, as applicable

5.1.3 Sampling and testing procedures, acceptance criteria (detailed description of, or reference to, established procedures, as described in pharmacopoeias)

5.1.4 Reporting

5.1.4.1 Calibration of test equipment used in the production process

5.1.4.2 Test data (raw data)

5.1.4.3 Results (summary)

5.1.5 Approval and requalification procedure

5.2 Subprocess 2 (same as for Subprocess 1)

5.n Subprocess n

Part 6. Product characteristics, test data from validation batches

Part 7. Evaluation, including comparison with the acceptance criteria and recommendations (including frequency of revalidation/ requalification)

Part 8. Certification (approval)

Part 9. If applicable, preparation of an abbreviated version of the validation report for external use, for example by the regulatory authority

The validation protocol and report may also include copies of the product stability report or a summary of it, validation documentation on cleaning, and analytical methods.

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[1] CIP = Cleaning in place/position
SIP = Sterilizing/steaming in place/position

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Annex 7
Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans

1. Introductory note

The legal status of investigational pharmaceutical products for human use varies from country to country; in some of them (e.g. Germany, the United States and others), these products are manufactured and inspected like "normal" licensed pharmaceutical products. In most other countries, however, they are not covered by legal and regulatory provisions in the areas of good manufacturing practice (GMP) inspection, etc.

However, the EC guide on GMP (*1*) recommends that the principles of GMP should be applied, as appropriate, to the preparation of these products, and the WHO guide on GMP, according to the statement in the general considerations, is applicable to "the preparation of clinical trials supplies" (*2*, page 18).

2. General considerations

The present guidelines supplement both the WHO guide on GMP and the guidelines on good clinical practice (GCP) for trials on pharmaceutical products (*3*). The application of the principles of GMP to the preparation of investigational products is necessary for several reasons:

- To assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials.
- To assure consistency between the investigational product and the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product.
- To protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilization, contamination and cross-contamination, mix-ups, wrong labelling, etc.), or from starting materials and components of inadequate quality.
- To document all changes in the manufacturing process.

In this context, the selection of an appropriate dosage for clinical trials is important. While it is accepted that in early trials the dosage form may be very different from the anticipated final formulation (e.g. a capsule instead of a tablet), in the pivotal Phase III studies it should be similar to

the projected commercial presentation; otherwise these trials will not necessarily prove that the marketed product is both efficacious and safe.

If there are significant differences between the clinical and commercial dosage forms, data should be submitted to the registration authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials. Final manufacturing methods must be revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.

This Annex specifically addresses those practices that may be different for investigational products, which are usually not manufactured in accordance with a set routine, and which may possibly be incompletely characterized during the initial stages of clinical development.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

clinical trial
Any systematic study on pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, and/or identify any adverse reaction to, investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally divided into Phases I-IV. It is not possible to draw clear distinctions between these phases, and different opinions about details and methodology do exist. However, the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, can be briefly defined as follows:

Phase I. These are the first trials of a new active ingredient or new formulations in humans, often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, and an initial pharmacokinetic/pharmacodynamic profile of the active ingredient.

Phase II. The purpose of these therapeutic pilot studies is to determine activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which it is intended. The trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. This phase is also concerned with the determination of appropriate dose ranges/regimens and (if possible) the clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

Phase III: This phase involves trials in large (and possibly varied) patient groups for the purpose of determining the short- and long-term safety-

efficacy balance of formulation(s) of the active ingredient, and assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated, and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect, such as age). The trials should preferably be randomized double-blind, but other designs may be acceptable, e.g. long-term safety studies. In general, the conditions under which the trials are conducted should be as close as possible to the normal conditions of use.

Phase IV. In this phase studies are performed after the pharmaceutical product has been marketed. They are based on the product characteristics on which the marketing authorization was granted and normally take the form of post-marketing surveillance, and assessment of therapeutic value or treatment strategies. Although methods may differ, the same scientific and ethical standards should apply to Phase IV studies as are applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc., are normally regarded as trials of new pharmaceutical products.

investigational product
Any pharmaceutical product (new product or reference product) or placebo being tested or used as a reference in a clinical trial.

investigator
The person responsible for the trial and for protecting the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person legally allowed to practise medicine/ dentistry.

monitor
A person appointed by, and responsible to, the sponsor for monitoring and reporting the progress of the trial and for the verification of data.

order
An instruction to process, package and/or ship a certain number of units of an investigational product.

pharmaceutical product
For the purpose of this Annex, this term is defined in the same way as in the WHO guidelines on GCP (*3*), i.e. as any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

product specification file(s)
Reference file(s) containing all the information necessary to draft the detailed written instructions on processing, packaging, labelling, quality control testing, batch release, storage conditions and shipping.

protocol
A document which gives the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. It should be dated and signed by the investigator/institution involved and the sponsor, and can, in addition, function as a contract.

shipping/dispatch
The assembly, packing for shipment, and sending of ordered medicinal products for clinical trials.

sponsor
An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

4. Quality assurance

Quality assurance of pharmaceutical products has been defined and discussed in detail in the guide on GMP (*2,* pages 25-26).

The quality of dosage forms in Phase III clinical studies should be characterized and assured at the same level as for routinely manufactured products. The quality assurance system, designed, established and verified by the manufacturer, should be described in writing, taking into account the GMP principles to the extent that they are applicable to the operations in question. This system should also cover the interface between the manufacture and the trial site (e.g. shipment, storage, occasional additional labelling).

5. Validation[1]

Some of the production processes for investigational products that have not received marketing authorization may not be validated to the extent necessary for a routine production operation. The product specifications and manufacturing instructions may vary during development. This increased complexity in the manufacturing operations requires a highly effective quality assurance system.

For sterile products, there should be no reduction in the degree of validation of sterilizing equipment required. Validation of aseptic processes presents special problems when the batch size is small, since the number of units filled may be not adequate for a validation exercise. Filling and sealing, which is often done by hand, can compromise the

[1] For additional advice on validation, see Annex 6.

maintenance of sterility. Greater attention should therefore be given to environmental monitoring.

6. Complaints

The conclusions of any investigation carried out in response to a complaint should be discussed between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, to determine the cause, and to take any necessary corrective action.

7. Recalls

Recall procedures should be understood by the sponsor, investigator and monitor in addition to the person(s) responsible for recalls, as described in the guide on GMP (*2*, pages 28-29).

8. Personnel

Although it is likely that the number of staff involved will be small, people should be separately designated as responsible for production and quality control. All production operations should be carried out under the control of a clearly identified responsible person. Personnel concerned with development, involved in production and quality control, need to be instructed in the principles of GMP.

9. Premises and equipment

During the manufacture of investigational products, different products may be handled in the same premises and at the same time, and this reinforces the need to eliminate all risks of contamination, including cross-contamination. Special attention should be paid to line clearance in order to avoid mix-ups. Validated cleaning procedures should be followed to prevent cross-contamination.

For the production of the particular products referred to in section 11.20 of the guide on GMP (*2*, page 38), campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account should be taken of the solubility of the product and excipients in various cleaning agents.

10. Materials

Starting materials

The consistency of production may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate,

microbiological properties should therefore be defined, documented in their specifications, and controlled. Existing compendial standards, when available, should be taken into consideration. Specifications for active ingredients should be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active ingredients should be periodically reassessed.

Detailed information on the quality of active and non-active ingredients, as well as of packaging materials, should be available so as to make it possible to recognize and, as necessary, allow for any variation in production.

Chemical and biological reference standards for analytical purposes

Reference standards from reputable sources (WHO or national standards) should be used, if available; otherwise the reference substance(s) for the active ingredient(s) should be prepared, tested and released as reference material(s) by the producer of the investigational pharmaceutical product, or by the producer of the active ingredient(s) used in the manufacture of that product.

Principles applicable to reference products for clinical trials

In studies in which an investigational product is compared with a marketed product, steps should be taken to ensure the integrity and quality of the reference products (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made in the product, data should be available (e.g. on stability, comparative dissolution) that demonstrate that these changes do not influence the original quality characteristics of the product.

11. Documentation

Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), master formulae, and processing and packaging instructions may be changed frequently as a result of new experience in the development of an investigational product. Each new version should take into account the latest data and include a reference to the previous version so that traceability is ensured. Rationales for changes should be stated and recorded.

Batch processing and packaging records should be retained for at least 2 years after the termination or discontinuance of the clinical trial, or after the approval of the investigational product.

Order

The order may request the processing and/or packaging of a certain number of units and/or their shipping. It may only be given by the sponsor to the manufacturer of an investigational product. It should be in

writing (though it may be transmitted by electronic means), precise enough to avoid any ambiguity and formally authorized, and refer to the approved product specification file (see below).

Product specification file(s)

A product specification file (or files) should contain the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping. It should indicate who has been designated or trained as the authorized person responsible for the release of batches (see reference *2*, page 18). It should be continuously updated while at the same time ensuring appropriate traceability to the previous versions.

Specifications

In developing specifications, special attention should be paid to characteristics which affect the efficacy and safety of pharmaceutical products, namely:

- The accuracy of the therapeutic or unitary dose: homogeneity, content uniformity.
- The release of active ingredients from the dosage form: dissolution time, etc.
- The estimated stability, if necessary, under accelerated conditions, the preliminary storage conditions and the shelf-life of the product.[1]

In addition, the package size should be suitable for the requirements of the trial.

Specifications may be subject to change as the development of the product progresses. Changes should, however, be made in accordance with a written procedure authorized by a responsible person and clearly recorded. Specifications should be based on all available scientific data, current state-of-the-art technology, and the regulatory and pharmacopoeial requirements.

Master formulae and processing instructions

These may be changed in the light of experience, but allowance must be made for any possible repercussions on stability and, above all, on bioequivalence between batches of finished products. Changes should be made in accordance with a written procedure, authorized by a responsible person and clearly recorded.

It may sometimes not be necessary to produce master formulae and processing instructions, but for every manufacturing operation or supply there should be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

[1] See Annex 5.

Packaging instructions

The number of units to be packaged should be specified before the start of the packaging operations. Account should be taken of the number of units necessary for carrying out quality controls and of the number of samples from each batch used in the clinical trial to be kept as a reference for further rechecking and control. A reconciliation should be carried out at the end of the packaging and labelling process.

Labelling instructions

The information presented on labels should include:

- The name of the sponsor.
- A statement: "for clinical research use only".
- A trial reference number.
- A batch number.
- The patient identification number.[1]
- The storage conditions.
- The expiry date (month/year) or a retest date.

Additional information may be displayed in accordance with the order (e.g. dosing instructions, treatment period, standard warnings). When necessary for blinding purposes, the batch number may be provided separately (see also "Blinding operations" on p. 106). A copy of each type of label should be kept in the batch packaging record.

Processing and packaging batch records

Processing and packaging batch records should be kept in sufficient detail for the sequence of operations to be accurately traced. They should contain any relevant remarks which increase existing knowledge of the product, allow improvements in the manufacturing operations, and justify the procedures used.

Coding (or randomization) systems

Procedures should be established for the generation, distribution, handling and retention of any randomization code used in packaging investigational products.

A coding system should be introduced to permit the proper identification of "blinded" products. The code, together with the randomization list, must permit proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation. The coding system must permit determination without delay in an emergency situation of the identity of the actual treatment product received by individual subjects.

[1] This is not necessarily inserted at the manufacturing facility but may be added at a later stage.

12. Production

Products intended for use in clinical trials (late Phase II and Phase III studies) should as far as possible be manufactured at a licensed facility, e.g.:

- A pilot plant, primarily designed and used for process development.
- A small-scale facility (sometimes called a "pharmacy")[1] separate both from the company's pilot plant and from routine production.
- A larger-scale production line assembled to manufacture materials in larger batches, e.g. for late Phase III trials and first commercial batches.
- The normal production line used for licensed commercial batches, and sometimes for the production of investigational pharmaceutical products if the number, e.g. of ordered ampoules, tablets or other dosage forms, is large enough.

The relation between the batch size for investigational pharmaceutical products manufactured in a pilot plant or small-scale facility to the planned full-size batches may vary widely depending on the pilot plant or "pharmacy" batch size demanded and the capacity available in full-size production.

The present guidelines are applicable to licensed facilities of the first and second types. It is easier to assure compliance with GMP in facilities of the second type, since processes are kept constant in the course of production and are not normally changed for the purpose of process development. Facilities of the remaining types should be subject to all GMP rules for pharmaceutical products.

Administratively, the manufacturer has yet another possibility, namely to contract out the preparation of investigational products. Technically, however, the licensed facility will be of one of the above-mentioned types. The contract must then clearly state, *inter alia*, the use of the pharmaceutical product(s) in clinical trials. Close cooperation between the contracting parties is essential.

Manufacturing operations

Validated procedures may not always be available during the development phase, which makes it difficult to know in advance what critical parameters and in-process controls would help to control these parameters. Provisional production parameters and in-process controls may then usually be deduced from experience with analogous products. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continuously to the experience gained in production.

[1] Some manufacturers use the term "pharmacy" to designate other types of premises, e.g. areas where starting materials are dispensed and batches compounded.

For sterile investigational products, assurance of sterility should be no less than for licensed products. Cleaning procedures should be appropriately validated and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

Packaging and labelling

The packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) when "blinded" labels are used than for licensed products. Supervisory procedures such as label reconciliation, line clearance, etc., and the independent checks by quality control staff should accordingly be intensified.

The packaging must ensure that the investigational product remains in good condition during transport and storage at intermediate destinations. Any opening of, or tampering with, the outer packaging during transport should be readily discernible.

Blinding operations

In the preparation of "blinded" products, in-process control should include a check on the similarity in appearance and any other required characteristics of the different products being compared.

13. Quality control

As processes may not be standardized or fully validated, end-product testing is more important in ensuring that each batch meets its specification.

Product release is often carried out in two stages, before and after final packaging:[1]

1. Bulk product assessment: this should cover all relevant factors, including production conditions, the results of in-process testing, a review of manufacturing documentation and compliance with the product specification file and the order.
2. Finished product assessment: this should cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the product specification file and the order.

When necessary, quality control should also be used to verify the similarity in appearance and other physical characteristics, odour, and taste of "blinded" investigational products.

[1] This practice also exists at certain large companies with regard to licensed products.

Samples of each batch of product should be retained in the primary container used for the study or in a suitable bulk container for at least 2 years after the termination or completion of the relevant clinical trial. If the sample is not stored in the pack used for the study, stability data should be available to justify the shelf-life in the pack used.

14. Shipping, returns, and destruction

The shipping, return and destruction of unused products should be carried out in accordance with the written procedures laid down in the protocol. All unused products sent outside the manufacturing plant should, as far as possible, either be returned to the manufacturer or destroyed in accordance with clearly defined instructions.

Shipping

Investigational products should be shipped in accordance with the orders given by the sponsor.

A shipment is sent to an investigator only after the following two-step release procedure: (i) the release of the product after quality control ("technical green light"); and (ii) the authorization to use the product, given by the sponsor ("regulatory green light"). Both releases should be recorded.

The sponsor should ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol.

A detailed inventory of the shipments made by the manufacturer should be maintained, and should make particular mention of the addressee's identification.

Returns

Investigational products should be returned under agreed conditions defined by the sponsor, specified in written procedures, and approved by authorized staff members.

Returned investigational products should be clearly identified and stored in a dedicated area. Inventory records of returned medicinal products should be kept. The responsibilities of the investigator and the sponsor are dealt with in greater detail in the WHO guidelines on GCP (*3*).

Destruction

The sponsor is responsible for the destruction of unused investigational products, which should therefore not be destroyed by the manufacturer without prior authorization by the sponsor. Destruction operations should be carried out in accordance with environmental safety requirements.

Destruction operations should be recorded in such a manner that all operations are documented. The records should be kept by the sponsor.

If requested to destroy products, the manufacturer should deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents should permit the batches involved to be clearly identified.

References

1. *Good manufacturing practice for medicinal products in the European Community.* Brussels, Commission of the European Communities, 1992.
2. 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).
3. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *The use of essential drugs. Model List of Essential Drugs (Eighth List). Sixth report of the WHO Expert Committee.* Geneva, World Health Organization, 1995:97-137 (WHO Technical Report Series, No. 850).

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Annex 8
Good manufacturing practices: supplementary guidelines for the manufacture of herbal medicinal products[1]

1. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

constituents with known therapeutic activity
Substances or groups of substances which are chemically defined and known to contribute to the therapeutic activity of a plant material or of a preparation.

herbal medicinal product
Medicinal product containing, as active ingredients, exclusively plant material and/or preparations. This term is generally applied to a finished product. If it refers to an unfinished product, this should be indicated.

markers
Constituents of a medicinal plant material which are chemically defined and of interest for control purposes. Markers are generally employed when constituents of known therapeutic activity are not found or are uncertain, and may be used to calculate the quantity of plant material or preparation in the finished product. When starting materials are tested, markers in the plant material or preparation must be determined quantitatively.

medicinal plant
A plant (wild or cultivated) used for medicinal purposes.

medicinal plant material (crude plant material, vegetable drug)
Medicinal plants or parts thereof collected for medicinal purposes.

plant preparations
Comminuted or powdered plant material, extracts, tinctures, fatty or essential oils, resins, gums, balsams, expressed juices, etc., prepared from plant material, and preparations whose production involves a fractionation, purification or concentration process, but excluding chemically defined isolated constituents. A plant preparation can be regarded as the active ingredient whether or not the constituents having therapeutic activities are known.

[1] Guidelines for the *assessment* of herbal medicines are provided in Annex 11.

2. General

Unlike conventional pharmaceutical products, which are usually prepared from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicinal products are prepared from material of plant origin which may be subject to contamination and deterioration, and may vary in composition and properties. Furthermore, in the manufacture and quality control of herbal medicinal products, procedures and techniques are often used which are substantially different from those employed for conventional pharmaceutical products.

The control of the starting materials, storage and processing assumes particular importance because of the often complex and variable nature of many herbal medicinal products and the number and the small quantity of defined active ingredients present in them.

3. Premises

Storage areas

Medicinal plant materials should be stored in separate areas. The storage area should be well ventilated and equipped in such a way as to protect against the entry of insects or other animals, especially rodents. Effective measures should be taken to limit the spread of animals and micro-organisms introduced with the plant material and to prevent cross-contamination. Containers should be located in such a way as to allow free air circulation.

Special attention should be paid to the cleanliness and good maintenance of the storage areas, particularly when dust is generated.

The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; steps should be taken to ensure that these conditions are provided and monitored.

Production area

To facilitate cleaning and to avoid cross-contamination whenever dust is generated, special precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g. by the use of dust extraction or dedicated premises.

4. Documentation

Specifications for starting materials

In addition to the data called for in sections 14 and 18 of "Good manufacturing practices for pharmaceutical products"(*1*), the specifications for medicinal plant materials should as far as possible include the following:

- The botanical name, with reference to the authors.
- Details of the source of the plant (country or region of origin, and where applicable, method of cultivation, time of harvesting, collection procedures, possible pesticides used, etc.).
- Whether the whole plant or only a part is used.
- When dried plant is purchased, the drying system.
- A description of the plant material based on visual and/or microscopical inspection.
- Suitable identification tests including, where appropriate, identification tests for known active ingredients or markers.
- The assay, where appropriate, of constituents of known therapeutic activity or markers.
- Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination.
- The results of tests for toxic metals and for likely contaminants, foreign materials and adulterants.
- The results of tests for microbial contamination and aflatoxins.

Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Instructions on the conduct of such procedures should be available and should include details of the process, tests and limits for residues.

Qualitative and quantitative requirements

These should be expressed in the following ways:

1. Medicinal plant material:
   (a) the quantity of plant material must be stated; or
   (b) the quantity of plant material may be given as a range, corresponding to a defined quantity of constituents of known therapeutic activity.

Example:

Name of active ingredient	*Quantity*
Sennae folium	(a) 900 mg or (b) 830–1000 mg, corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B

2. Plant preparation:
   (a) the equivalent quantity or the ratio of plant material to plant preparation must be stated (this does not apply to fatty or essential oils); or
   (b) the quantity of the plant preparation may be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see example).

The composition of any solvent or solvent mixture used and the physical state of the extract must be indicated.

If any other substance is added during the manufacture of the plant preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) must be described as "other ingredients" and the genuine extract as the "active ingredient".

Example:

Name of active ingredient	*Quantity*
Sennae folium	(a) 125 mg ethanolic extract (8:1) or 125 mg ethanolic extract, equivalent to 1000 mg of Sennae folium or (b) 100–130 mg ethanolic extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B
Other ingredient	
Dextrin	20–50 mg

Specifications for the finished product

The control tests for the finished product must be such as to allow the qualitative and quantitative determination of the active ingredients. If the therapeutic activity of constituents is known, this must be specified and determined quantitatively. When this is not feasible, specifications must be based on the determination of markers.

If either the final product or the preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the combined content of several active ingredients may be determined. The need for such a procedure must be justified.

Processing instructions

The processing instructions should list the different operations to be performed on the plant material, such as drying, crushing and sifting, and also include the temperatures required in the drying process, and the methods to be used to control fragments or particle size. Instructions on sieving or other methods of removing foreign materials should also be given. Details of any process, such as fumigation, used to reduce microbial contamination, together with methods of determining the extent of such contamination, should also be given.

For the production of plant preparations, the instructions should specify any vehicle or solvent that may be used, the times and temperatures to be observed during extraction, and any concentration methods that may be required.

5. Quality control

The personnel of quality control units should have particular expertise in herbal medicinal products to be able to carry out identification tests, and check for adulteration, the presence of fungal growth or infestations, lack of uniformity in a consignment of medicinal plant materials, etc.

Reference samples of plant materials must be available for use in comparative tests, e.g. visual and microscopic examination and chromatography.

Sampling

Sampling must be carried out with special care by personnel with the necessary expertise since medicinal plant materials are composed of individual plants or parts of plants and are therefore heterogeneous to some extent.

Further advice on sampling, visual inspection, analytical methods, etc., is given in *Quality control methods for medicinal plant materials* (2).

6. Stability tests

It will not be sufficient to determine the stability only of the constituents with known therapeutic activity, since plant materials or plant preparations in their entirety are regarded as the active ingredient. It must also be shown, as far as possible, e.g. by comparisons of chromatograms, that the other substances present are stable and that their content as a proportion of the whole remains constant.

If a herbal medicinal product contains several plant materials or preparations of several plant materials, and it is not feasible to determine the stability of each active ingredient, the stability of the product should be determined by methods such as chromatography, widely used assay methods, and physical and sensory or other appropriate tests.

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992:44-52; 75-76 (WHO Technical Report Series, No. 823).

2. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1992 (unpublished document WHO/PHARM/92.559/rev. 1; available on request from Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland).

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Annex 9
Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Introduction

Multisource (generic) drug products must satisfy the same standards of quality, efficacy and safety as those applicable to 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, obviously including parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by the implementation of good manufacturing practices (GMP) 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 products manufactured by biotechnology, the concept of interchangeability raises complex considerations that are not addressed here, and these products will consequently not be considered. 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 should be included in the documentation submitted with the application 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. On the basis of these suggestions, WHO convened three consultations during 1993 and 1994 in Geneva which led to the formulation of the present guidelines. Participants at the consultations included representatives of drug regulatory authorities, the universities, and the pharmaceutical industry, including the generic industry.

The objective of these guidelines 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 by the WHO Tuberculosis Programme and the International Union against Tuberculosis and Lung Disease. This states, *inter alia,* 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". Fixed-dosage combinations containing rifampicin must therefore 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 in the WHO Model List of Essential Drugs. WHO will assist small regulatory authorities, for whom these guidelines are 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 the interchangeability of multisource products within both an international and a national context by proposing the establishment of international reference materials as comparators for bioequivalence testing.

These guidelines apply to the marketing of pharmaceutical products intended to be therapeutically equivalent and thus interchangeable (generics) but produced by different manufacturers. They should be interpreted and applied without prejudice to the obligations incurred through existing international agreements on trade-related aspects of intellectual property rights (*1*).

Glossary

The 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 determined from appropriate studies (bioequivalence, pharmacodynamic, clinical or *in vitro* studies).

generic product

The term "generic product" has somewhat different meanings in different jurisdictions. In this document, therefore, use of this term is avoided as much as possible, and the term "multisource pharmaceutical product" (see definition below) is used instead. 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" has 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 the 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; if they meet the same or comparable standards; and if they 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 that it has been authorized for marketing and its efficacy, safety and quality have been established and documented.

Part One. Regulatory assessment of interchangeable multisource pharmaceutical products

1. General considerations

The national health authorities (national drug regulatory authorities) should ensure that all pharmaceutical products subject to their control are in conformity with acceptable standards of quality, safety and efficacy, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with GMP standards so as to ensure the continued conformity of the products with 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 the licensing of their manufacturers, importing agents and distributors exists and adequate resources are available for implementation. Health authorities in countries with limited resources are less able to perform these tasks. To assure the quality of imported pharmaceutical products and drug substances, they are therefore 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 (*2*) in the exporting country, is most effectively obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (see Annex 10), which provides a channel of communication between the regulatory authorities in the importing and exporting countries (see World Health Assembly resolutions WHA41.18 and WHA45.29).

The essential functions and responsibilities of a drug regulatory authority have been further elaborated by WHO in the guiding principles for small national drug regulatory authorities (*3, 4*).

2. Multisource products and interchangeability

Economic pressures often favour the use of generic products, and this can sometimes result in the purchase on contract of such products by

procurement agencies without prior licensing by the appropriate drug regulatory authority. However, all pharmaceutical products, including generic products, should be used in a country only after approval by that 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 those intended for the domestic market in that 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 without effect on 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 therefore require the documentation of a generic pharmaceutical product to meet three sets of criteria relating to:

- manufacture (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 is not required in a particular case. Types of *in vivo* studies 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 so that *in vivo* studies are therefore required.

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 containing established ingredients, the following information, *inter*

alia, should be provided in the documentation submitted with the application for marketing authorization and for inclusion in a computerized data retrieval system:

- the name of the product;
- the active ingredient(s) (designated by their international nonproprietary name(s)), their source, and a description of the manufacturing methods and the in-process controls;
- the type of dosage form;
- the route of administration;
- the main therapeutic category;
- a complete quantitative formula with justification and the method of manufacture of the dosage form in accordance with WHO GMP (*2*);
- quality control specifications for the starting materials, intermediates and final dosage form product, together with a validated analytical method;
- the results of batch testing together with the batch number and date of manufacture, including, where appropriate, the batch(es) used in bioequivalence studies;
- the indications, dosage and method of use;
- the contraindications, warnings, precautions and drug interactions;
- use in pregnancy and in other special groups of patients;
- the adverse effects;
- the effects and treatment of overdosage;
- equivalence data (comparative bioavailability, pharmacodynamic or clinical studies and comparative *in vitro* dissolution tests);
- stability data, proposed shelf-life, and recommended storage conditions;
- the container, packaging and labelling, including the proposed product information;
- the proposed method of distribution, e.g. as a controlled drug or a prescription item, and whether the product is intended for pharmacy sale or for general sale;
- the manufacturer and the licensing status (date of most recent inspection, date of licence and the authority that issued the licence);
- the importer/distributor;
- the regulatory status in the exporting country and, where available, summary of regulatory assessment documents from the exporting country, as well as the regulatory status in other countries.

If the dosage form is a novel one intended to modify drug delivery, e.g. 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, and the

content of this information should be approved as a part of the marketing authorization. It should be updated in the light of current information. The wording and illustrations used in the subsequent promotion of the product should be fully consistent with this approved product information. All promotional activities should satisfy the WHO ethical criteria for medicinal drug promotion (see World Health Assembly resolution WHA41.17, 1988).

5. Collaboration between drug regulatory authorities

Bilateral or multilateral collaboration between drug regulatory authorities assists countries with limited resources. Sharing responsibilities in assessment and increasing mutual cooperation provide a wider spectrum of expertise for evaluation. Harmonization of the registration requirements for generics of the various drug regulatory authorities 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, the exchange of evaluation reports between drug regulatory authorities on the same product from the same manufacturer can accelerate sound decision-making at the national level. Such an exchange should take place only subject to the agreement of the company concerned. Appropriate measures for safeguarding data confidentiality must be taken.

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 for assessing equivalence, including:

- Comparative bioavailability (bioequivalence) studies in humans, in which the active drug substance or one or more metabolites is measured in an accessible biological fluid such as plasma, blood or urine.
- Comparative pharmacodynamic studies in humans.
- Comparative clinical trials.
- *In vitro* dissolution tests.

The applicability of each of these four methods is discussed in subsequent sections of these guidelines and special guidance is provided

on assessing bioequivalence studies. Other methods have also been used to assess bioequivalence, e.g. bioequivalence studies in animals, but are not discussed here because they have not been accepted worldwide.

The acceptance of any test procedure in the documentation of the equivalence of two pharmaceutical products by a drug regulatory authority depends on many factors, including the characteristics of the active drug substance and the drug product, and the availability of the resources necessary for the conduct of a specific type of study. Where a drug produces meaningful concentrations in an accessible biological fluid, such as plasma, bioequivalence studies are preferred. Where a drug does not produce measurable concentrations in such a 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).

Other criteria that indicate when equivalence studies are, or are not, necessary are discussed in sections 8 and 9 below.

8. When equivalence studies are not necessary

The following types of multisource pharmaceutical products are considered to be equivalent without the need for further documentation:

(a) products to be administered parenterally (e.g. by the intravenous, intramuscular, subcutaneous or intrathecal route) as aqueous solutions that contain the same active substance(s) in the same concentration(s) and the same excipients in comparable concentrations;
(b) solutions for oral use that contain the active substance in the same concentration and do not contain an excipient that is known or suspected to affect gastrointestinal transit or absorption of the active substance;
(c) gases;
(d) powders for reconstitution as a solution when the solution meets either criterion (a) or criterion (b) above;
(e) otic or ophthalmic products prepared as aqueous solutions that contain the same active substance(s) in the same concentration(s) and essentially the same excipients in comparable concentrations;
(f) topical products prepared as aqueous solutions that contain the same active substance(s) in the same concentration(s) and essentially the same excipients in comparable concentrations;
(g) inhalation products or nasal sprays that are administered with or without essentially the same device, are prepared as aqueous solutions, and contain the same active substance(s) in the same concentration(s) 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 requirements (e), (f) and (g) above, it is incumbent on the applicant to demonstrate that the excipients in the multisource product are essentially the same as, and are present in concentrations comparable to, those in the reference product. If 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 listed in section 8, it is recommended in these guidelines that documentation of equivalence should be requested by registration authorities for multisource pharmaceutical products. In such documentation, the product should be compared with 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 include:

(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, non-linear pharmacokinetics, presystemic elimination/high first-pass metabolism >70%;
   (iv) unfavourable physicochemical properties, e.g. low solubility, instability, metastable modifications, poor permeability;
   (v) documented evidence for bioavailability problems related either to the drug itself or to drugs of similar chemical structure or formulation;
   (vi) high ratio of excipients to active ingredients;

(b) non-oral and non-parenteral pharmaceutical products designed to act by systemic absorption (e.g. transdermal patches, suppositories);

(c) sustained-release and other types of modified-release pharmaceutical products designed to act by systemic absorption;

(d) fixed combination products (*4*) with systemic action;

(e) non-solution pharmaceutical products for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc.) and intended to act without systemic absorption. The concept of bioequivalence is then not

applicable, 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.

For the first four types of pharmaceutical products, plasma concentration measurements over time (bioequivalence) are normally sufficient proof of efficacy and safety. For the last type, as already pointed out, the bioequivalence concept is not applicable, and comparative clinical or pharmacodynamic studies are required to prove equivalence.

In vitro studies

For certain drugs and dosage forms (see also section 13), equivalence may be assessed by means of *in vitro* dissolution testing. This may be considered acceptable for example for:

(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, and:

- the qualitative composition of the different strengths is essentially the same;
- the ratio of active ingredients to excipients for the different strengths is essentially the same or, for low 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 the case of systemic availability, pharmacokinetics have been shown to be linear over the therapeutic dose range.

Although these guidelines are concerned primarily with the registration requirements for multisource pharmaceutical products, it should be noted that *in vitro* dissolution testing may also be suitable for use in confirming that product quality and performance characteristics have remained unchanged following minor changes in formulation or manufacture 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 guidelines for good clinical practice for trials on pharmaceutical products (*5*) (see box), with GMP (*2*) and with good laboratory practice (GLP) (*6*).

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 or benefits of a particular clinical trial be thoroughly considered and that the chosen options 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. Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) or non-maleficence (doing no harm), as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects[1] or the 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

Pre-clinical studies that provide sufficient documentation of the potential safety of a pharmaceutical product for the intended investigational use are a prerequisite for a clinical trial. Information about manufacturing procedures and data from tests performed on the actual product should establish that it is of suitable quality for the intended investigational use. The pharmaceutical, pre-clinical and clinical data should be appropriate to the 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 the safety and efficacy of the investigational product obtained in previous and ongoing clinical trials is required for planning and conducting subsequent trials.

1.4 Investigator and site(s) of investigation

Each investigator should have appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the clinical trial, the investigator(s) and the sponsor should establish an agreement on the protocol, standard operating procedures (SOP), the monitoring and auditing of the trial, and the allocation of trial-related responsibilities. The trial site should be adequate to enable the trial to be conducted safely and efficiently.

1.5 Regulatory requirements

Countries in which clinical trials are performed should have regulations governing the way in which these studies can be conducted. The pre-trial agreement between the sponsor and investigator(s) should designate the parties responsible for meeting each applicable regulatory requirement (e.g. application to or notification of the trial to the relevant authority, amendments to the trial protocol, reporting of adverse events and reactions, and notifications to the ethics committee). All parties involved in a clinical trial should comply fully with the existing national regulations or requirements. In countries where regulations do not exist or require supplementation, relevant

[1] These guidelines are updated regularly by the Council for International Organizations of Medical Sciences (CIOMS).

government officials may designate, in part or in whole, these Guidelines as the basis on which clinical trials will be conducted. The use of these Guidelines should not prevent their eventual adaptation into national regulations or laws. Neither should they be used to supersede an existing national requirement in countries where the national requirement is more rigorous.

2. **The protocol**

The clinical trial should be carried out in accordance with a written 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 to the protocol as amendments.

The protocol, appendices and any other relevant documentation should state the aim of the trial and the procedures to be used; the reasons for proposing that the trial should be undertaken on humans; 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, appendices and other relevant documentation should be reviewed from a scientifc and ethical standpoint by one or more (if required by local laws and regulations) review bodies (e.g. institutional review board, peer review committee, ethics committee or drug regulatory authority), constituted appropriately for this purpose and independent of the investigator(s) and sponsor.

For additional information, see the guidelines for good clinical practice for trials on pharmaceutical products (5), from which the above text has been taken.

10. Bioequivalence studies in humans

Bioequivalence studies are designed to compare the *in vivo* performance of a test multisource pharmaceutical product with that of a reference pharmaceutical product. A common design for a bioequivalence study involves the administration of the test and reference products on two occasions to volunteer subjects, the second administration being separated from the first by a wash-out period of duration such as to ensure that drug given in the first treatment is entirely eliminated before the second treatment is administered. Just before administration and for a suitable period afterwards, blood and/or urine samples are collected and assayed for the 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 indication 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 (including

plasma or serum) and/or urine concentration-time curves are used to calculate certain bioequivalence metrics of interest. Commonly used metrics include the area under the blood (plasma or serum) concentration-time curve (AUC) and the peak concentration. These are calculated for each subject in the study and the resulting values compared statistically. Details of the general approach are given below.

Subjects

Selection of subjects

The subject population for bioequivalence studies should be as homogeneous as possible; studies should therefore generally be performed with healthy volunteers so that variability, other than in the pharmaceutical products concerned, is reduced. Clear criteria for inclusion/exclusion should be established. If possible, subjects should be of both sexes; however, the risk to women will need to be considered on an individual basis and, if necessary, they should be warned of any possible dangers to the fetus if they should become pregnant. They should normally be in the age range 18–55 years and of weight within the normal range according to accepted life tables. Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If smokers are included, they should be identified as such. Volunteers should be screened for suitability by means of 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 drug being investigated.

If the aim of the bioequivalence study is to address specific questions (e.g. bioequivalence in a special population), the selection criteria will have to be adjusted accordingly.

Genetic phenotyping

Phenotyping and/or genotyping of subjects may be considered for safety reasons.

Patients versus healthy volunteers

If the active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to use patients under treatment instead. 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 the 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 is conducted.

Design

General study design

The study should be designed so that the test conditions are such as to reduce intra- and intersubject variability and avoid biased results. Standardization of exercise, diet, fluid intake and posture, and restriction of the intake of alcohol, caffeine, certain fruit juices, and drugs other than that being studied in the period before and during the study are important in order to minimize the variability of all the factors involved except that of the pharmaceutical product(s) being tested.

A cross-over design with randomized allocation of volunteers to each leg is the first choice for bioequivalence studies. Study design should, however, depend on the type of drug, and other designs may be more appropriate in certain cases, e.g. with highly variable drugs and those with a long half-life. In cross-over studies, a wash-out period between the administration of the test product and that of the reference product of more than five times the half-life of the dominant drug is usual, but special consideration will need to be given to extending this period if active metabolites with longer half-lives are produced, and also under certain other circumstances.

The administration of the test product should be standardized, i.e. the time of day for ingestion and the volume of fluid (150 ml is usual) should be specified. Test products are usually administered 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 commonly used to assess the extent and rate of absorption. Sampling points or periods should be chosen such that the time-concentration profile is adequately defined so as to allow the calculation of relevant parameters. From the primary results, the bioavailability parameters desired, e.g. AUC_∞, AUC_t, C_{max}, t_{max}, Ae_∞, Ae_t, dAe/dt, or any other necessary parameters, are derived (see Appendix 2). The method of calculating AUC-values should be specified. AUC_∞ and C_{max} are considered to be the most useful parameters for the assessment of bioequivalence. For urine excretion data, the corresponding parameters are Ae_∞ and dAe/dt_{max}. For additional information, $t_{1/2}$ and MRT can be calculated, and for steady-state studies, AUC_τ, and the per cent peak-trough fluctuation. 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

For drugs which would cause unacceptable pharmacological effects (e.g. serious adverse events) in volunteers or where the drug is toxic or particularly potent or the trial necessitates a high dose, cross-over or parallel-group studies in patients may be required.

Drugs with long half-lives may require a parallel design or the use of truncated area under curve (AUC_t) data or a multidose study. The truncated area should cover the absorption phase.

For drugs for which the rate of input into the systemic circulation is important, more samples may have to be collected around the time t_{max}.

Multidose studies may be helpful in assessing bioequivalence for:

- drugs with non-linear kinetics (including those with saturable plasma protein binding);
- drugs for which the assay sensitivity is too low to cover a large enough portion of AUC_∞;
- drug substance combinations, if the ratio of the plasma concentration 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, safety and efficacy. It should be calculated by appropriate methods (see p. 131) and should not normally be smaller than 12. In most studies, 18–24 subjects will be needed (*7–9*). The number of subjects recruited should always be justified.

Investigational products

The products (samples) used in bioequivalence studies for registration purposes should be identical to the projected commercial pharmaceutical product. For this reason, not only the composition and quality characteristics (including stability) but also the methods of manufacture should be those to be used in future routine production runs.

Samples should ideally be taken from industrial-scale batches. When this is not feasible, pilot- or small-scale production batches may be used provided that they are not less than one-tenth (10%) of the size of the expected full-scale production batches.

It is recommended that the potency and *in vitro* dissolution characteristics of the test and reference pharmaceutical products should be ascertained before an equivalence study is performed. The content of active drug substance(s) in the two products should not differ by more than ±5%. If the potency of the reference material deviates by more than 5% from that corresponding to the declared content of 100%, 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

The use of metabolite data in bioequivalence studies requires careful consideration. The evaluation of bioequivalence will generally be based on the measured concentrations of the pharmacologically active drug substance and its active metabolite(s), if present. If it is impossible to measure the concentration of the active drug substance, that of a major biotransformation product may be measured instead, while measurement of the concentration of such a 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, that of an 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, however, assays that distinguish between the enantiomers of a chiral drug substance may be appropriate.

Validation of analytical procedures

All analytical procedures must be well characterized, fully validated and documented, and satisfy the relevant requirements as to specificity, accuracy, sensitivity and precision. Knowledge of the stability of the active substance and/or biotransformation product in the sample material is a prerequisite for obtaining reliable results (*10*). It should be noted that:

- validation comprises both 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 procedures; the revalidation study must be documented usually as an appendix to the study report;
- within a given 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, the samples from these studies have been assayed by different methods, and the methods cover a similar concentration range and the same matrix, they should be cross-validated.

The results of validation should be reported.

Reserve samples

Sufficient samples of each batch of the pharmaceutical products used in the studies, together with a record of their analyses and characteristics,

must be kept for reference purposes under appropriate storage conditions as specified by national regulations. At the specific request of the competent authorities, these reserve samples may be handed over to them so that they can recheck the products.

Statistical analysis and acceptance criteria

General consideration

The primary concern in bioequivalence assessment is to limit the risk (α) of a false declaration of equivalence to that which the regulatory authorities are willing to accept.

The statistical methods of choice at present are the two one-sided tests procedure (*11*) and the derivation of a parametric or non-parametric $100(1-2\alpha)\%$ confidence interval for the quotient μ_T/μ_R of the test and reference pharmaceutical products. The value of α 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 interval (*12, 13*).

The statistical procedures should be specified before data collection starts (see Appendix 3), and should lead to a decision scheme which is symmetrical with respect to the two formulations, i.e. it should lead to the same decision whether the new formulation is compared with the reference product or vice versa.

Concentration and concentration-related quantities e.g. AUC and C_{max}, should be analysed after logarithmic transformation, but 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, when descriptive statistics should be given that do not require specific distributional assumptions, e.g. medians instead of means.

The assumptions underlying the design or analysis should be addressed, and the possibility of differing variations in the formulations should be investigated. This covers the investigation of period effects, sequence or carry-over effects, and homogeneity of variance.

The impact of outlying observations on the conclusions should be reviewed. Medical or pharmacokinetic explanations for such observations should be sought.

Acceptance ranges

For AUC, the 90% confidence interval should generally be within the acceptance range 80-125%. For drugs with a particularly narrow therapeutic range, the AUC acceptance range may need to be smaller; this should be justified clinically.

C_{max} does not characterize the rate of absorption particularly well in many cases, but 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 that for AUC (see Appendix 3).

Reporting of results

The report on a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation in compliance with the guidelines on good clinical practice (GCP) for trials on pharmaceutical products (*5*). The responsible investigator(s) should sign the respective section(s) of the report. The names and affiliations of the responsible investigator(s), the site of the study and the 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 also be given. The analytical validation report should be attached. The results of *in vitro* dissolution tests should be provided. In addition, the applicant for registration should submit a signed statement confirming that the test product is identical with the pharmaceutical product submitted.

All results should be clearly presented. 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 scale, and may also be shown on a linear/log scale. All individual data and results should be given, including those for any subjects who have dropped out of the trial. Drop-out and withdrawal of subjects should be reported and accounted for. Test results on representative samples should be included.

The statistical report should be sufficiently detailed 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

Pharmacodynamic measurements in healthy volunteers or patients may be used for establishing equivalence between two pharmaceutical products. This may be necessary if the drug and/or its metabolite(s) in plasma or urine cannot be determined quantitatively with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurements of drug concentrations cannot be used as surrogate end-points for the demonstration of the efficacy and safety of the particular pharmaceutical product; this applies, for example, to topical products where it is not intended that the drug should be absorbed into the systemic circulation.

If pharmacodynamic studies are used, the conditions under which they are performed must be as rigorously controlled as those of bioequivalence studies, and the requirements of the guidelines for good clinical practice (GCP) for trials on pharmaceutical products (5) must be satisfied.

The following requirements must be taken into account in planning, conducting and assessing the results of a study intended to demonstrate equivalence by means of measurements of pharmacodynamic drug responses:

- the response measured should be a pharmacological or therapeutic effect 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 maximum response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses that produce 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 by means of a suitable instrument on a repetitive basis to provide a record of the pharmacodynamic events which are substitutes for plasma concentrations; where such measurements are not possible, recordings on visual analogue scales may be used, and 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, and the criteria whereby responders and non-responders are identified must be stated in the protocol;
- where an important placebo effect can occur, allowance for this effect should be made in the study design by including placebo treatment as a third phase in that design;
- the underlying pathology and natural history of the condition should be considered in the study design, and information on the reproducibility of baseline conditions should be available;
- where a cross-over design is not appropriate, a parallel group study design should be chosen.

In studies in which continuous variables can 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 are measured, and parameters can be derived which describe the area under the effect-time curve, the maximum response and the time when that response occurred.

The statistical methods for the assessment of the outcome of the study are, in principle, the same as those outlined for bioequivalence studies. However, a correction should be made for the potential non-linearity of

the relationship between the dose and the area under the effect-time curve, based on the outcome of a dose-response study. However, it should be noted that the conventional acceptance range as applied for bioequivalence assessment is usually too large and therefore not appropriate; for this reason, it should be defined on a case-by-case basis and described in the protocol.

12. Clinical trials

For certain drugs and dosage forms (see example (e), pp. 123-124) plasma concentration time-profile data are not suitable for use in assessing equivalence between two formulations. While pharmacodynamic studies can sometimes be an appropriate tool for establishing equivalence (see section 11), in other instances this type of study cannot be performed because of a lack of meaningful and measurable pharmacodynamic parameters; a comparative clinical trial must then be performed in order to demonstrate equivalence between two formulations. In such a clinical trial, the same statistical principles will apply as in 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 that required in bioequivalence studies.

The methodology to be used in establishing equivalence between pharmaceutical products by means of a clinical trial in patients in which there is a therapeutic end-point has not yet been discussed as extensively as that used in bioequivalence trials. However, the following are important and need to be defined in the protocol:

(a) The target parameters; these are usually relevant clinical end-points from which the intensity and the onset, if applicable and relevant, of the response can be derived.

(b) The size of the acceptance range; this must be defined on a case-by-case basis, taking into consideration the specific clinical conditions, for example 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 used), 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 statistical method used; this is currently the confidence interval approach, the main concern being to rule out the possibility that the test product is inferior to the reference pharmaceutical product by more than the specified amount. A one-sided confidence interval (for efficacy and/or safety) may therefore be appropriate. The confidence intervals can be derived by either parametric or non-parametric methods.

Where appropriate, a placebo leg should be included in the design, and it is sometimes appropriate 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. However, because of the many limitations associated with the use of *in vitro* dissolution in the documentation of equivalence it is recommended in these guidelines that its application for this purpose should be kept to a minimum. *In vitro* dissolution testing as the sole documentation of equivalence is therefore not applicable to the drugs and dosage forms listed as examples (a)-(e) on p. 123, but should be reserved for rapidly dissolving drug products.[1] When the 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 by the use of comparative *in vitro* dissolution studies should be based on the generation of comparative dissolution profiles rather than single-point dissolution tests, as described in various pharmacopoeial compendia and other publications. 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 useful in product development and in monitoring the batch-to-batch consistency of the manufacturing process following approval of marketing. Such tests are also used to check the consistency of the release characteristics of a dosage form during storage. Dissolution testing may also provide a useful check on a number of characteristics of the dosage form, including:

– the particle size distribution, state of hydration, crystal form and other solid state properties of the active ingredients;

[1] Where a drug substance and drug product do not dissolve with sufficient rapidity, as noted above, *in vitro* dissolution methods may still be used to document equivalence using appropriately validated dissolution methodology including an *in vitro/in vivo* correlation. Such methodology should be derived from the development and application of specifications and statistical methods to define non-equivalence. This may require formulations with different *in vivo* performance characteristics. With such formulations, discriminatory *in vitro* dissolution tests for use in equivalence studies may be developed. With these additional requirements, however, a standard *in vivo* bioequivalence study as described in section 7 may be preferable.

– the mechanical properties of the dosage 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 on *in vitro* dissolution should be provided in the documentation submitted with the application for marketing authorization. *In vitro* dissolution tests and quality control specifications 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 preapproval period in accordance with 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). The use of smaller batches should be justified. Material from these test batches is used to provide material both for dissolution studies and for equivalence testing. Physiologically relevant media and test conditions should be used for dissolution tests on these batches. When selecting the test methods to be used, it is recommended that widely used compendial methods ("paddle" and "basket") should be used initially and other methods ("flow-through cell", etc.) tried if these fail to demonstrate sufficient discriminatory power. Dissolution profiles are recommended, even when a single-point compendial dissolution test is available. For immediate-release pharmaceutical products, a single-point dissolution test may be used for quality control purposes. Specifications for the dissolution performance of batches subsequently manufactured will be based on the results of the dissolution tests performed on the test batches. While it is undisputed that the value of dissolution testing will be increased if the test results can be shown by *in vivo* studies to reflect important changes in formulation and/or the manufacturing process, the practical problems involved are still under discussion. It is not recommended that the dissolution specification should be made less stringent on the basis of the performance of the test batches beyond the point where equivalence between the test material used in the equivalence study and production batches subsequently manufactured can no longer be assumed.

The following data should be recorded and included in the documentation submitted with the application for marketing authorization:

(a) comparative dissolution results for the test and reference pharmaceutical products after intervals appropriate for the products and conditions under investigation (a minimum of three sampling times is normal);
(b) for each sampling time, the observed data, individual values, the range and the coefficient of variation (relative standard deviation).

Part Five. Clinically important variations in bioavailability leading to non-approval of the product

A new formulation of bioavailability outside the acceptance range as compared with an existing pharmaceutical product is by definition not interchangeable. A marketing authorization for a formulation of lower bioavailability may not be approved because of efficacy concerns. In contrast, a formulation of higher bioavailability ("suprabioavailability") may not be approved because of safety concerns. There are then the following two options:

1. The suprabioavailable dosage form, if reformulated so as to be bioequivalent to the existing pharmaceutical product, could be accepted as interchangeable with that product. This may not be ideal, however, as dosage forms of lower bioavailability tend to be variable in performance.
2. A dosage form of increased bioavailability in which the content of active substance has been appropriately reduced could be accepted as a new (improved) dosage form, but this decision 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 be such as to preclude confusion with the older approved pharmaceutical product(s).

Part Six. Studies needed to support new post-marketing manufacturing conditions

With all pharmaceutical products, when post-marketing changes are made, extensive *in vitro* and/or *in vivo* testing may be required. Such changes may be in: (i) formulation; (ii) site of manufacture; (iii) manufacturing process; and (iv) manufacturing equipment. The types and extent of the further testing required will depend on the magnitude of the changes made. If a major change is made, the product might then become a new pharmaceutical product, if the national regulatory 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 reference products, which are selected at national level by the drug regulatory authority. Either the most widely used "leading" pharmaceutical product in the market or the product that was first approved in that market is normally chosen. It is therefore possible that significant differences may exist between the reference products adopted in different countries.

This being so, consideration needs to be given to the feasibility of developing reference products 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 of defined quality and bioavailability.

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Appendix 1

Examples of national requirements for *in vivo* equivalence 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 requirements for 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 1. 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 the USA do not require 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, also 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, 5 mg	+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. 124-135.

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 valerate	cream, 0.1% of betamethasone	+p	+p+c	+p
	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

[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. 124–135.

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, 50 mg	+b	+b	+b
clomipramine hydrochloride	capsule, 10 mg, 25 mg	+b	o	+b
cloxacillin sodium	capsule, 500 mg of cloxaxillin	?	+b	+b
codeine phosphate	tablet, 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. 124-135.
[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 (50 000 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, 30 µg + 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	-	o	-
	tablet, 60 mg of Fe + folic acid, 250 µg	-	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. 124-135.
[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, 40 mg	+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 IU/ml in 10-ml vial,	+b	-	+b+p
	80 IU/ml in 10-ml vial,	+b	-	+b+p
	100 IU/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 (intermediate-acting)	100 IU of insulin/ml in 10-ml vial	+b	-	+b+p
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: 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. 124-135.

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 acetate (depot)	injection, 150 mg/ml in 1-ml vial,	?	+*b	+b
	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

[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. 124–135.

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. 124-135.

Table 1 (*continued*)
Examples of national requirements for equivalence studies[1]

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, 10 mg	+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 hydrate	–	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. 124–135.

Table 1 (*continued*)
Examples of national requirements for equivalence studies[1]

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
proguanil 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 tablet, 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. 124-135.

Table 1 (*continued*)
Examples of national requirements for equivalence studies[1]

Drug substance	Dosage form	Canada	Germany	USA
rifampicin	capsule, 150 mg, 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, 150 mg	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, 200 mg, 500 mg	+b	+b	+b
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, 20 mg of tamoxifen	+b	+b	+b
testosterone enantate	injection, 200 mg in 1-ml ampoule	?	+b	-
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. 124–135.

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	o
	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. 124-135.

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}	The minimum plasma concentration.
C_{max}-ratio	The ratio of the 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 value of AUC may be that for a specific period, e.g. AUC from zero to 12 hours is shown as 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) under steady-state conditions.
AUC-ratio	The ratio of the 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 is shown as Ae_{12}.
Ae_t	*Ae* from zero to the last quantifiable concentration.
Ae_∞	*Ae* from zero to infinite time, obtained by extrapolation.
Ae_τ	*Ae* over one dosing interval under steady-state conditions.
d*Ae*/d*t*	The rate of urinary excretion 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 between the arithmetic means of the test and reference t_{max} values.
$t_{1/2}$	The plasma (serum, whole blood) half-life.
MRT	The mean residence time.
μ_T	Average bioavailability 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 in the methods specified for the statistical evaluation is acceptable only if adherence to the protocol would preclude a meaningful evaluation and if such a change in procedure has been fully justified.

Concentration-dependent data such as AUC and C_{max} should be log transformed before statistical analysis in order to satisfy the fundamental assumption underlying analysis of variance that effects in the model act 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 80-125% (see p. 131). If the 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} makes sense only if there is a clinically relevant claim for rapid release or action, or signs of a relation to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

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Annex 10
Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

1. Provisions and objectives

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 on an 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

[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.

resolution WHA28.65 (*2*), and a second revision of the requirements is included in the thirty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (*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 the 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 WHO, in writing, of:

- its willingness to participate in the Scheme;
- any significant reservations it intends to observe relating to this participation; and
- the name and address of its national drug authority or other competent authority.

2.2 These notifications are subsequently announced in the monthly *WHO pharmaceuticals 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 WHO.

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 the 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.
- The 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 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.

3. Requesting a certificate

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

– a Certificate of 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 Appendices 1, 2 and 3 of these guidelines. To facilitate their use, they are presented in forms suitable for generation by computer. All participating countries are henceforth urged to adopt these formats to facilitate the 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 the certification of information going beyond the scope of the Scheme. When manufacture takes place in a country other than that where the product certificate is issued, an attestation that such manufacture complies 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. While they are not part of the documents, they should always be attached to them.

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 of 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:

- the name and dosage form of the product;
- the name and the amount of active ingredient(s) per unit dose (the International Nonproprietary Name(s), where such exist(s), should be used);
- the name and address of the product-licence holder and/or manufacturing facility;

– the formula (the complete qualitative composition including all excipients); this is particularly important 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 section 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 in 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 The Statement of Licensing Status of Pharmaceutical Product(s) (Appendix 2) 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 (Appendix 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 requirement in tender and procurement documents.

3.15 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 that it may deem relevant. Translation by an applicant of these materials into a widely used language, preferably English, shall be deemed to satisfy the provisions of section 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 forming 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 by the importing country, an identical copy, clearly marked as duplicate, should be forwarded by the certifying authority directly to that country's 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.

References

1. Quality control of drugs. In: *Twenty-second World Health Assembly, Boston, Massachusetts, 8-25 July 1969. Part I: Resolutions and decisions, annexes.* Geneva, World Health Organization, 1969: 99-105 (Official Records of the World Health Organization, No. 176).
2. Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *Twenty-eighth World Health Assembly, Geneva, 13-30 May 1975. Part 1: Resolutions and decisions, annexes.* Geneva, World Health Organization, 1975: 94-95 (Official Records of the World Health Organization, No. 226).
3. 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).
4. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *Forty-first World Health Assembly, Geneva, 2-13 May 1988. Resolutions and decisions, annexes.* Geneva, World Health Organization, 1988: 53-55 (document WHA41/1988/REC/1).

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 qualitative 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 are:[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 note 8*)

2B.2.1 For categories b and c the name and address of the manufacturer producing the dosage form are:[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 number: _____ 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 be provided only 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 must be updated or it will cease to be 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 a Summary of Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission must 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 that 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 7 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 WordPerfect 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:

Telephone/fax numbers:

Name of authorized person:

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 WordPerfect from the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Appendix 3

Model Batch Certificate of a Pharmaceutical Product

Manufacturer's/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 the 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 the exporting countries.

Name and address of authorized person:

_____

_____

Telephone number: _____ 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, the 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 WordPerfect 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, terms used in the guidelines are explained here and/or reference is made to relevant sections. This appendix provides supplementary information and is not a formal part of the Scheme.

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

abuse of Scheme
See sections 4.9 and 5.2 of the guidelines.

active ingredients
See sections 1.5, 4.4 and 4.5 of the guidelines.

addresses of competent authorities
See sections 2.2 and 3.3 of the guidelines.

applicant
The party applying for a Product Certificate. This is normally the product-licence holder. Because certain data are confidential for commercial reasons, the competent authority in the exporting country must always 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 section 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 Appendix 3 of the guidelines, will normally be issued for each batch by the manufacturer. Furthermore, a batch certificate may exceptionally be validated or issued by the competent authority of the exporting country, particularly for vaccines, sera and other biological products. The batch certificate accompanies 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
The competent authority that issues product certificates. It must ensure that it possesses the capacities listed in section 2.4 of the guidelines.

charges for product certificates
See section 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 section 2.1 of the guidelines). The competent authority can issue or receive certificates.

WHO makes available on 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 sections 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 section 3.2 of the guidelines.

GMP certificate
See section 3.2 of the guidelines.

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

language of product certificate
See section 3.10 of the guidelines.

licence holder
An individual or a corporate entity possessing a marketing authorization for 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 certificate by competent authority
See sections 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 section 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 section 4.7 of the guidelines and item 2A.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 the 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 the 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 on to the market.

registration certificate
See *product licence*.

specifications
See Appendix 3, explanatory note 7.

statement of licensing status
See section 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 of 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 section 4.6 of the guidelines.

WHO responsibility
See section 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).

WHO Technical Report Series, No. 863, 1996

Annex 11
Guidelines for the assessment of herbal medicines[1, 2]

Introduction

For the purpose of these guidelines, herbal medicines are defined as follows:

> Finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines.
>
> Exceptionally, in some countries herbal medicines may also contain, by tradition, natural organic or inorganic active ingredients which are not of plant origin.

The past decade has seen a significant increase in the use of herbal medicines. As a result of WHO's promotion of traditional medicine, countries have been seeking the assistance of the Organization in identifying safe and effective herbal medicines for use in national health care systems.

In 1991, the Director-General of WHO, in a report to the Forty-fourth World Health Assembly, emphasized the great importance of medicinal plants to the health of individuals and communities. Earlier, in 1978, the Thirty-first World Health Assembly had adopted a resolution (WHA31.33) that called on the Director-General to compile and periodically update a therapeutic classification of medicinal plants, related to the therapeutic classification of all drugs; subsequently, resolution WHA40.33, adopted in 1987, urged Member States to ensure quality control of drugs derived from traditional plant remedies by using

---

[1] Adapted from WHO document WHO/TRM/91.4. These guidelines were finalized at a WHO consultation in Munich, Germany, 19-21 June 1991. The request for WHO to prepare the guidelines came from the Fifth International Conference of Drug Regulatory Authorities (ICDRA) held in Paris in 1989. The finalized guidelines were presented to the Sixth ICDRA in Ottawa in 1991.

[2] Guidelines for the *manufacture* of herbal medicines are provided in Annex 8.

modern techniques and applying suitable standards and good manufacturing practices; and resolution WHA42.43, of 1989, urged Member States to introduce measures for the regulation and control of medicinal plant products and for the establishment and maintenance of suitable standards. Moreover, the International Conference on Primary Health Care, held in Alma-Ata, USSR, in 1978, recommended, *inter alia*, the accommodation of proven traditional remedies in national drug policies and regulatory measures.

In developed countries, a resurgence of interest in herbal medicines has resulted from the preference of many consumers for products of natural origin. In addition, manufactured herbal medicines often follow in the wake of migrants from countries where traditional medicines play an important role.

In both developed and developing countries, consumers and health care providers need to be supplied with up-to-date and authoritative information on the beneficial properties, and possible harmful effects, of all herbal medicines.

The Fourth International Conference of Drug Regulatory Authorities, held in Tokyo in 1986, organized a workshop on the regulation of herbal medicines moving in international commerce. Another workshop on the same subject was held as part of the Fifth International Conference of Drug Regulatory Authorities, held in Paris in 1989. Both workshops confined their considerations to the commercial exploitation of traditional medicines through over-the-counter labelled products. The Paris meeting concluded that the World Health Organization should consider preparing model guidelines containing basic elements of legislation designed to assist those countries wishing to develop appropriate legislation and registration.

The objective of these guidelines is to define basic criteria for the evaluation of quality, safety and efficacy of herbal medicines and thereby to assist national regulatory authorities, scientific organizations and manufacturers to undertake an assessment of the documentation/submissions/dossiers in respect of such products. As a general rule in this assessment, traditional experience means that long-term use as well as the medical, historical and ethnological background of those products shall be taken into account. The definition of long-term use may vary according to the country but should be at least several decades. Therefore, the assessment should take into account a description in the medical/pharmaceutical literature or similar sources, or a documentation of knowledge on the application of a herbal medicine without a clearly defined time limitation. Marketing authorizations for similar products should be taken into account.

Prolonged and apparently uneventful use of a substance usually offers testimony of its safety. In a few instances, however, investigation of the potential toxicity of naturally occurring substances widely used as

ingredients in these preparations has revealed previously unsuspected potential for systematic toxicity, carcinogenicity and teratogenicity. Regulatory authorities need to be quickly and reliably informed of these findings. They should also have the authority to respond promptly to such alerts, either by withdrawing or varying the licences of registered products containing suspect substances, or by rescheduling the substances to limit their use to medical prescription.

Assessment of quality

Pharmaceutical assessment

This should cover all important aspects of the quality assessment of herbal medicines. It should be sufficient to make reference to a pharmacopoeial monograph if one exists. If no such monograph is available, a monograph must be supplied and should be set out as in an official pharmacopoeia.

All procedures should be in accordance with good manufacturing practices.

Crude plant material

The botanical definition, including genus, species and authority, should be given to ensure correct identification of a plant. A definition and description of the part of the plant from which the medicine is made (e.g. leaf, flower, root) should be provided, together with an indication of whether fresh, dried or traditionally processed material is used. The active and characteristic constituents should be specified and, if possible, content limits should be defined. Foreign matter, impurities and microbial content should be defined or limited. Voucher specimens, representing each lot of plant material processed, should be authenticated by a qualified botanist and should be stored for at least a 10-year period. A lot number should be assigned and this should appear on the product label.

Plant preparations

Plant preparations include comminuted or powdered plant materials, extracts, tinctures, fatty or essential oils, expressed juices and preparations whose production involves fractionation, purification or concentration. The manufacturing procedure should be described in detail. If other substances are added during manufacture in order to adjust the plant preparation to a certain level of active or characteristic constituents or for any other purpose, the added substances should be mentioned in the manufacturing procedures. A method for identification and, where possible, assay of the plant preparation should be added. If identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (e.g. "chromatographic fingerprint") to ensure consistent quality of the preparation.

Finished product

The manufacturing procedure and formula, including the amount of excipients, should be described in detail. A finished product specification should be defined. A method of identification and, where possible, quantification of the plant material in the finished product should be defined. If the identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (e.g. "chromatographic fingerprint") to ensure consistent quality of the product. The finished product should comply with general requirements for particular dosage forms.

For imported finished products, confirmation of the regulatory status in the country of origin should be required. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be applied.

Stability

The physical and chemical stability of the product in the container in which it is to be marketed should be tested under defined storage conditions and the shelf-life should be established.

Assessment of safety

This should cover all relevant aspects of the safety assessment of a medicinal product. A guiding principle should be that, if the product has been traditionally used without demonstrated harm, no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment.

A review of the relevant literature should be provided with original articles or references to the original articles. If official monograph/review results exist, reference can be made to them. However, although long-term use without any evidence of risk may indicate that a medicine is harmless, it is not always certain how far one can rely solely on long-term usage to provide assurance of innocuity in the light of concern expressed in recent years over the long-term hazards of some herbal medicines.

Reported side-effects should be documented according to normal pharmacovigilance practices.

Toxicological studies

Toxicological studies, if available, should be part of the assessment. Literature should be indicated as above.

Documentation of safety based on experience

As a basic rule, documentation of a long period of use should be taken into consideration when assessing safety. This means that, when there are no detailed toxicological studies, documented experience of long-term

use without evidence of safety problems should form the basis of the risk assessment. However, even in cases of drugs used over a long period, chronic toxicological risks may have occurred but may not have been recognized. The period of use, the health disorders treated, the number of users and the countries with experience should be specified. If a toxicological risk is known, toxicity data must be submitted. The assessment of risk, whether independent of dose or related to dose, should be documented. In the latter case, the dosage specification must be an important part of the risk assessment. An explanation of the risks should be given, if possible. Potential for misuse, abuse or dependence must be documented. If long-term traditional use cannot be documented or there are doubts on safety, toxicity data should be submitted.

Assessment of efficacy

This should cover all important aspects of efficacy assessment. A review of the relevant literature should be carried out and copies provided of the original articles or proper references made to them. Research studies, if they exist, should be taken into account.

Activity

The pharmacological and clinical effects of the active ingredients and, if known, their constituents with therapeutic activity should be specified or described.

Evidence required to support indications

The indication(s) for the use of the medicine should be specified. In the case of traditional medicines, the requirements for proof of efficacy should depend on the kind of indication. For treatment of minor disorders and for non-specific indications, some relaxation in requirements for proof of efficacy may be justified, taking into account the extent of traditional use. The same considerations may apply to prophylactic use. Individual experiences recorded in reports from physicians, traditional health practitioners or treated patients should be taken into account.

Where traditional use has not been established, appropriate clinical evidence should be required.

Combination products

As many herbal remedies consist of a combination of several active ingredients, and as experience of the use of traditional remedies is often based on combination products, assessment should differentiate between old and new combination products. Identical requirements for the assessment of old and new combinations would result in inappropriate assessment of certain traditional medicines.

In the case of traditionally used combination products, the documentation of traditional use (such as classical texts of Ayurveda, traditional Chinese medicine, Unani, Siddha) and experience may serve as evidence of efficacy.

An explanation of a new combination of well known substances, including effective dose ranges and compatibility, should be required in addition to the documentation of traditional knowledge of each single ingredient. Each active ingredient must contribute to the efficacy of the medicine.

Clinical studies may be required to justify the efficacy of a new ingredient and its positive effect on the total combination.

Intended use

Product information for the consumer

Product labels and package inserts should be understandable to the consumer or patient. The package information should include all necessary information on the proper use of the product.

The following elements of information will usually suffice:

- name of the product
- quantitative list of active ingredient(s)
- dosage form
- indications
  - dosage (if appropriate, specified for children and the elderly)
  - mode of administration
  - duration of use
  - major adverse effects, if any
  - overdosage information
  - contraindications, warnings, precautions and major drug interactions
  - use during pregnancy and lactation
- expiry date
- lot number
- holder of the marketing authorization.

Identification of the active ingredient(s) by the Latin botanical name, in addition to the common name in the language of preference of the national regulatory authority, is recommended.

Sometimes not all information that is ideally required may be available, so drug regulatory authorities should determine their minimal requirements.

Promotion

Advertisements and other promotional material directed to health personnel and the general public should be fully consistent with the approved package information.

Utilization of these guidelines

These guidelines for the assessment of herbal medicines are intended to facilitate the work of regulatory authorities, scientific bodies and industry in the development, assessment and registration of such products. The assessment should reflect the scientific knowledge gathered in that field. Such assessment could be the basis for future classification of herbal medicines in different parts of the world. Other types of traditional medicines in addition to herbal products may be assessed in a similar way.

The effective regulation and control of herbal medicines moving in international commerce also requires close liaison between national institutions that are able to keep under regular review all aspects of production and use of herbal medicines, as well as to conduct or sponsor evaluative studies of their efficacy, toxicity, safety, acceptability, cost and relative value compared with other drugs used in modern medicine.

WHO Technical Report Series, No. 863, 1996

Annex 12
Guidelines on import procedures for pharmaceutical products

1. Introductory notes

1.1 Public health considerations demand that pharmaceutical products should not be treated in the same way as ordinary commodities. Their manufacture and subsequent handling within the distribution chain, both nationally and internationally, must conform to prescribed standards and be rigorously controlled. These precautions serve to assure the quality of authentic products, and to prevent the infiltration of illicit products into the supply system.

1.2 Within the context of its revised drug strategy, adopted in 1986 by the Thirty-ninth World Health Assembly in resolution WHA39.27, WHO developed "Guiding principles for small national drug regulatory authorities" (*1, 2*) which established a regulatory approach in line with the resources available within a small national regulatory authority, and were intended to assure not only the quality, but also the safety and efficacy, of pharmaceutical products distributed under its aegis.

1.3 The principles emphasize the need for the effective use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. This constitutes a formal agreement between participating Member States to provide information on any product under consideration for export, notably on its registration status in the country of origin and whether or not the manufacturer complies with WHO's guidelines on good manufacturing practices (GMP) for pharmaceutical products (*3*).

1.4 To be fully effective, the Scheme needs to be complemented by administrative and other safeguards aimed at ensuring that consignments of imported products are in conformity in all particulars with the relevant import licence and that they remain secure within the distribution chain. Storage and transit facilities must be proof against tampering and adverse climatic conditions, and relevant controls must be applied at every stage of transportation.

1.5 Pharmaceutical products containing substances controlled under the international conventions have long been subjected to rigorous border controls. Some of these controls, and particularly those designed to prevent the diversion and illicit interchange of products during transit, are relevant to all pharmaceutical products, and are therefore included in these guidelines. Full details of the special import controls required for narcotic drugs and psychotropic substances are given in the Appendix.

2. Objectives and scope

2.1 The following guidelines, which stem from the above considerations, have been developed in consultation with national drug regulatory authorities, the pharmaceutical industry, the World Customs Organization, and the United Nations International Drug Control Programme.

2.2 The guidelines are directed to all parties involved in the importation of pharmaceutical products, including national drug regulatory authorities, competent trade ministries, customs authorities, port authorities, and importing agents.

2.3 They are intended to promote efficiency in applying relevant regulations, to simplify the checking and handling of consignments of pharmaceutical products in international transit and, *inter alia*, to provide a basis for collaboration between the various interested parties.

2.4 They are applicable to any pharmaceutical product destined for use within the country of import, and are intended to be adapted to prevailing national conditions and legal requirements.

3. Legal responsibilities

3.1 The importation of pharmaceutical products should be effected in conformity with regulations promulgated under the national drugs act or other relevant legislation and enforced by the national drug regulatory authority. National guidelines providing recommendations on the implementation of these regulations should be drawn up by the national drug regulatory authority in collaboration with the customs authority and other interested agencies and organizations.

3.2 All transactions relating to the importation of consignments of pharmaceutical products should be conducted either through the governmental drug procurement agency or through independent wholesale dealers specifically designated and licensed by the national drug regulatory authority for this purpose.

3.3 The importation of all consignments of pharmaceutical products should be channelled exclusively through customs posts specifically designated for this purpose.

3.4 All formalities undertaken on importation should be coordinated by the customs service, which should have the authority to request the services of an official pharmaceutical inspector as occasion demands. When justified by the workload, a pharmaceutical inspector may be stationed full time at one or more of the designated ports of entry.

3.5 The customs authority should have the discretionary powers to request technical advice and opinions from other appropriately qualified persons, should this be warranted by particular circumstances.

4. Legal basis of control

4.1 Subject to the exemptions specified in paragraph 4.4 below, only pharmaceutical products proved by appropriate documentation to be duly licensed for marketing within the importing country should be cleared by customs.

4.2 The national drug regulatory authority should compile comprehensive and frequently updated lists of licensed products and authorized importing agents, and issue notifications of any product licences withdrawn on grounds of safety; the latter should be rapidly communicated and presented in a manner designed to attract attention. All lists and notifications of withdrawal of a product licence should be accessible, preferably through a computerized database, to designated customs posts, authorized importing agents and all drug wholesalers.

4.3 Efficient and confidential channels for communicating information on counterfeit products and other illicit activities should be established between all interested official bodies.

4.4 In countries where no formal system of product licensing has been established, importation of products is most effectively controlled by issuing permits in the name of the national drug regulatory authority to the authorized importing agency or agent. Additional measures that may be taken under these conditions include:

- the provision by the national drug regulatory authority to the customs authorities, and to the importing agency and agents, of official lists of pharmaceutical products permitted and/or prohibited to be imported;
- the provision by the importing agent of certified information to establish that the product is authorized by licence for sale in the country of export.

4.5 The national drug regulatory authority should reserve discretionary powers to waive product licensing requirements in respect of consignments of pharmaceutical products imported in response to emergency situations and, exceptionally, in response to requests from clinicians for limited supplies of an unlicensed product needed for the treatment of a specific named patient.

5. Required documentation

5.1 As a prerequisite to customs clearance, the importing agency or agent should be required to furnish the customs authority with the following documentation in respect of each consignment:

- certified copies of documents issues by the national drug regulatory authority in the importing country, attesting that:
  (a) the importer is duly authorized by licence to undertake the transaction; and
  (b) the product is duly authorized by licence to be marketed in the importing country;

- a batch certificate issued by the manufacturer, consonant with the requirements of the WHO Certification Scheme, that documents the results of the final analytical control of the batch(es) constituting the consignment;
- a relevant invoice or bill and, when applicable, an authorization for the release of foreign exchange granted by the competent national authority in the country of import;
- any other documentation required by national legislation for customs clearance.

6. Implementation of controls

6.1 A visual and physical examination should be routinely undertaken by the customs authorities, if possible in collaboration with an inspector of the national drug regulatory authority. The size of the consignment should be checked against invoices, and particular attention should be accorded to the nature and condition of the packaging and labelling.

6.2 Arrangements should be made with the inspector of the national drug regulatory authority for the routine sampling and subsequent analysis of exceptionally large and/or valuable consignments and any other consignment that has apparently deteriorated, or that is damaged or of doubtful authenticity.

6.3 When samples are taken for analysis to a governmental or other accredited drug quality control laboratory, the consignment should be placed in quarantine. During this procedure, and throughout the time that the consignment is held in customs, particular care must be taken to ensure that packages do not come into contact with potential contaminants.

6.4 A consignment suspected of being counterfeit should be placed in quarantine pending the analysis of samples and forensic investigation. Time is often saved if materials and reagents needed to undertake simple analytical tests are available at the port of entry.

6.5 Representatives of the manufacturer of the authentic product, and/or the owner of the trademark, and the consignee should immediately be advised of such action.

6.6 National regulations should define the responsibilities of the interested parties and the precise procedures to be followed. In particular, the provisions should identify the agency responsible for coordinating the investigation and bringing prosecutions.

6.7 Counterfeit or other products which have been imported in contravention of the law must be forfeited and destroyed, or otherwise dealt with in accordance with legal procedures.

6.8 The relevant authorities must be indemnified against any consequent legal actions and proceedings.

6.9 National drug regulatory authorities are urged to notify other national authorities of confirmed cases of imported counterfeit pharmaceutical products through the Division of Drug Management and Policies of WHO.

7. Procedures applicable to pharmaceutical starting materials

7.1 In accordance with good manufacturing practices, formal responsibility for the analytical control of starting materials is vested in the manufacturer of the finished pharmaceutical product. Consequently, few countries have introduced formal licensing requirements for active pharmaceutical substances.

7.2 Exceptionally, however, some national authorities now exercise documentary and, in some cases, analytical control of starting materials as a prerequisite to customs clearance.

7.3 Each imported consignment of a pharmaceutical starting material should be accompanied by a warranty (or batch certificate) prepared by the manufacturer as recommended by the WHO Certification Scheme.

8. Storage facilities

8.1 Many pharmaceutical products tend to degrade on storage and some need to be kept in cold storage. All customs posts designated to handle consignments of pharmaceutical products should consequently be provided with secure storage facilities, including refrigerated compartments. If no pharmaceutical inspector is employed on site, these facilities should be inspected periodically by the national drug regulatory authority to ensure that all equipment is maintained in good working order.

8.2 The importing agency or agent should alert the customs authorities in advance of the anticipated arrival of consignments in order that they may be transferred from the international carrier to the designated storage facility with the minimum of delay and, in appropriate cases, without breaking the cold chain.

8.3. Consignments of pharmaceutical products and pharmaceutical starting materials should be accorded high priority for clearance through customs.

8.4 When several different consignments await clearance, the customs authorities should be guided by the drug inspector as to which should be accorded priority.

9. Training requirements

9.1 Performance in implementing the guidelines should be reviewed on an open-ended basis and, if necessary, improved in the light of on-site

monitoring and evaluation. Workshops designed to facilitate efficient implementation of the guidelines and to foster collaborative approaches between the various responsible parties should be organized, as circumstances demand, by the national drug regulatory authority in collaboration with the customs authority.

References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990:64-79 (WHO Technical Report Series, No. 790).
2. *The use of essential drugs. Model List of Essential Drugs (Seventh List). Fifth report of the WHO Expert Committee.* Geneva, World Health Organization, 1992:62-74 (WHO Technical Report Series, No. 825).
3. 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).

Glossary

The definitions given apply to the terms used in these guidelines. They may have different meanings in other contexts.

authorization
See Note.

counterfeit product
A pharmaceutical product that is deliberately and fraudulently mislabelled with respect to identity and/or source. Both branded and generic products can be counterfeited, and counterfeit products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with insufficient quantity of active ingredients or with fake packaging.

drug regulatory authority
The national agency responsible for the registration of, and other regulatory activities concerning, pharmaceutical products.

import authority
The national agency responsible for authorizing imports (e.g. the ministry or department of trade or of imports and exports).

importation
The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

importer
An individual or company or similar legal entity importing or seeking to import a pharmaceutical product. A "licensed" or "registered" importer is one who has been granted a licence or registration status for the purpose. In addition to a general licence or permit as an importer, some countries require an additional licence to be issued by the national drug regulatory authority if pharmaceutical products are to be imported.

licence
See Note.

pharmaceutical product
Any medicine intended for human or veterinary use, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

registration
See Note.

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

Note
Because of a lack of uniformity in national legal requirements and administrative practices, the terms "registered", "licenced" and "authorized" have been used in these guidelines as if they were interchangeable. When the guidelines are being used as a basis for drawing up national guidelines, more precise terminology applicable to the country concerned should be used. In some countries, for example, "certificate of drug registration" has been replaced by terms such as "marketing authorization".

Appendix

Special import controls for narcotic drugs and psychotropic substances[1]

In accordance with the requirements of the international drug control treaties (i.e. the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 Protocol, and the Convention on Psychotropic Substances, 1971, referred to subsequently as the 1961 Convention and the 1971 Convention), each state must adopt national legislation and administrative regulations, and establish administrative structures to ensure the full implementation of the provisions of these treaties on its territory and cooperation with other states.

Most of the requirements specified in these guidelines on import procedures for pharmaceutical products also apply to the border control of narcotic drugs and psychotropic substances. In addition, detailed information on the control of international trade in narcotic drugs and psychotropic substances can be found in Article 31 of the 1961 Convention and Article 12 of the 1971 Convention respectively. The guidelines provided in this Appendix are intended to facilitate the operation of control at entry points, and can be expanded by taking into account the legislation and administrative regulations in force in each country.

The customs authorities and, if applicable, any other law enforcement authorities assigned to border control should cooperate closely with the competent authorities for the control of narcotic drugs and psychotropic substances designated by the government (subsequently referred to as the competent authorities). It should be noted that, while the competent authorities in some countries are different from the national drug regulatory authority, in others they may be one and the same.

The customs authorities, or any other competent law enforcement authorities, should be well trained and equipped (e.g. with drug identification kits) so that they can distinguish consignments of narcotic drugs and psychotropic substances from other pharmaceutical products. They should be provided with lists of narcotic drugs and psychotropic substances under international control, e.g. the "Yellow List" and "Green List" published by the International Narcotics Control Board, which include, *inter alia*, trade names of pharmaceutical products containing narcotic drugs and psychotropic substances. They may also make use of the *Multilingual dictionary of narcotic drugs and psychotropic substances under international control* (ST/NAR/1/REV.1) published by the United Nations (sales number E/F/S.93.XI.2). Furthermore, they

[1] "Narcotic drug" means any of the substances listed in Schedules I and II of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, whether natural or synthetic; "psychotropic substance" means any substance, natural or synthetic, listed in Schedule I, II, III or IV of the Convention on Psychotropic Substances, 1971.

should be provided with lists of narcotic drugs and psychotropic substances whose importation into the country has been prohibited.

Checks conducted during the border control of narcotic drugs and of psychotropic substances listed in Schedules I and II of the 1971 Convention should ensure that each consignment has been duly authorized by the competent authorities of the importing country. The competent authorities express their consent to each import by issuing an import certificate (for narcotic drugs) or an import authorization (for psychotropic substances). When presented with the original of this document, the competent authorities of the exporting country may issue an export authorization permitting the consignment containing narcotic drugs or psychotropic substances to leave the exporting country. In free ports and zones governments should exercise the same supervision and control as in other parts of their territory, provided, however, that they may apply more drastic measures if appropriate.

The competent authorities of the importing country may wish to inform the customs, or any other competent law enforcement authorities, of authorized imports of narcotic drugs and psychotropic substances before the entry of the consignment into the country.

In addition to the other documents referred to in section 5 of the guidelines, the customs authorities should require the importer or importer's agent to provide them with a copy of the respective import authorization (certificate) issued by the competent authorities of the importing country. This document should be compared with the export authorization issued by the competent authorities of the exporting country, a copy of which must accompany each consignment. The authenticity of these documents must be carefully checked. In case of doubt, the competent authorities should be consulted immediately.

Import and export authorizations (certificates) should contain the following information:

- the name of the narcotic drug or psychotropic substance (if available, the International Nonproprietary Name);
- the quantity to be imported/exported, expressed in terms of anhydrous base content;
- the pharmaceutical form and, if in the form of a preparation, the name of the preparation;
- the name and address of the importer and exporter;
- the period of validity of the authorization.

In addition, the export authorization should contain the number and date of the corresponding import authorization/certificate and the name of the competent authority of the importing country by whom it was issued.

The competent authorities of the importing country may wish to specify in the import authorization/certificate the entry point through which the importation must be effected.

During the visual and physical examination of the imported consignment, the quantity of narcotic drugs or psychotropic substances contained in it should be carefully checked. If the quantity exceeds the amount authorized, the consignment should be stopped by the customs and the matter brought to the attention of the competent authorities for the control of narcotic drugs and psychotropic substances in the importing country. If the quantity imported is the same as, or less than, the amount authorized, the quantity should be recorded on the copy of the export authorization accompanying the consignment and communicated to the competent authorities of the importing country.

All consignments containing psychotropic substances included in Schedule III of the 1971 Convention must be accompanied by a separate export declaration. This document should indicate the name and address of the exporter and importer, the name of the substance, the quantity and the pharmaceutical form in which the substance is exported, including, if applicable, the name of the preparation and the date of dispatch.

Pursuant to the recommendations contained in resolutions of the Economic and Social Council of the United Nations, many governments now require import authorizations not only for psychotropic substances in Schedules I and II but also for those in Schedules III and IV of the 1971 Convention. This strengthening of the control requirements has proved to be very useful in preventing attempts to divert psychotropic substances, such as stimulants, sedative-hypnotics and tranquillizers, into illicit traffic.