WHO Technical Report Series

863

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Thirty-fourth Report

World Health Organization

Geneva 1996

WHO Library Cataloguing in Publication Data

WHO Expert Committee on Specifications for Pharmaceutical Preparations
(34th : 1994 : Geneva, Switzerland)
WHO Expert Committee on Specifications for Pharmaceutical
Preparations : thirty-fourth report.

(WHO technical report series ; 863)

1. Drug industry 2. Drugs – standards 3. Quality control 4. Legislation, Drug 5. Guidelines
I. Title II. Series

ISBN 92 4 120863 5 (NLM Classification: QV 771)
ISSN 0512-3054

Printed in Switzerland
95/10779 – Benteli – 6700

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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.

Acknowledgements

Special acknowledgement was made by the Committee to Miss M. Schmid, Quality Assurance, Dr S. Kopp-Kubel, Regulatory Support, and Dr J. Idänpään-Heikkilä of the Division of Drug Management and Policies, WHO, Geneva, Switzerland, who were instrumental in the preparation and proceedings of the meeting.

The Committee also acknowledged with thanks the valuable contributions made to its work by the following institutions and persons:

WHO Collaborating Centre for Drug Quality Control, Therapeutic Goods Administration Laboratories, Department of Community Services and Health, Woden, Australian Capital Territory, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institute for the Control of Pharmaceutical and Biological Products, Temple of Heaven, Beijing, China; WHO Collaborating Centre for

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WHO Technical Report Series, No. 863, 1996

Annex 1
Guidelines for the graphic representation of chemical formulae

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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:

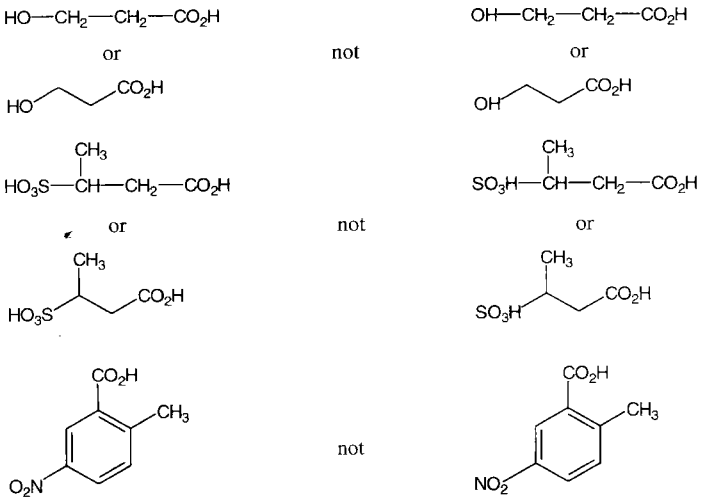
$-CH_3$ methyl	$-CHO$ formyl	$-CO_2H$ carboxy	$-CO_2^-$ carboxylate	$-CN$ cyano
$-NC$ isocyano	$-OH$ hydroxy	$-OCH_3$ methoxy	$-SO_3H$ sulfo	$-SO_3^-$ sulfonate
$-NH_2$ amino	$-NO_2$ nitro	$-N_3$ azido		

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

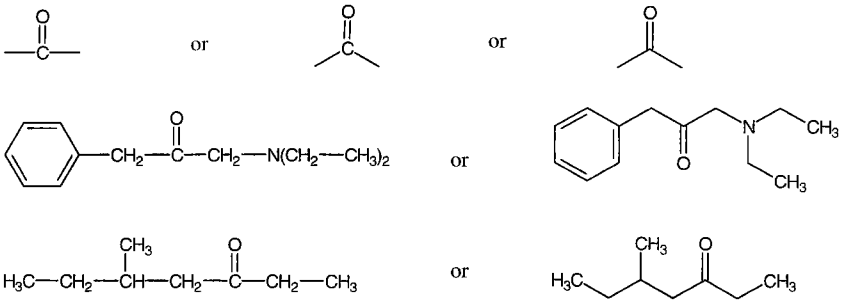
1.7 The bulky group *tert*-butyl (1,1-dimethylethyl) is often shown as $-C(CH_3)_3$. Hydroxymethyl and aminomethyl groups can be represented in either expanded or condensed form:

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

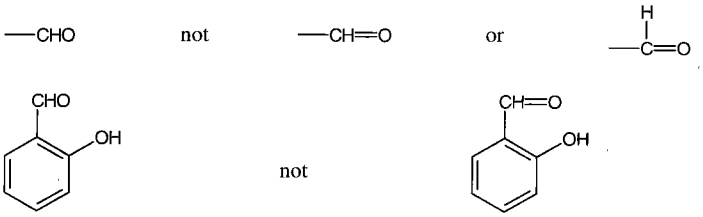
1.8 A polyatomic group is set out such that the atom that is directly attached to the rest of the structure is shown closest to the connecting dash:



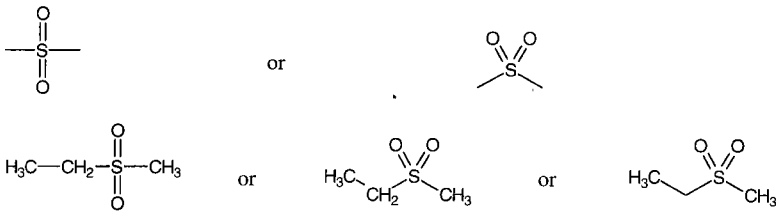
1.9 The carbonyl group in ketones is depicted as:



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

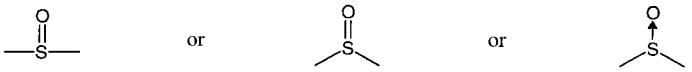


1.10 The sulfonyl group is depicted as:

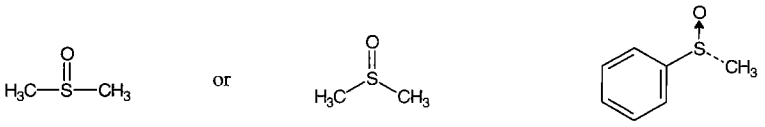


rather than in the condensed form —SO_2—

The sulfinyl group is shown as:



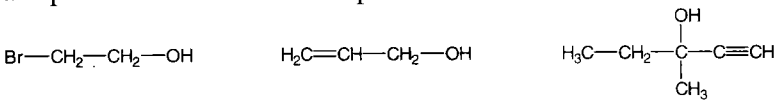
rather than in the condensed form —SO—; the last representation is useful as a means of recognizing a chiral compound:



2. Acyclic structures

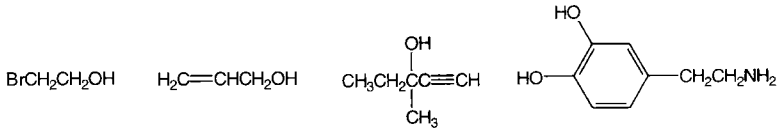
2.1 In acyclic structures, a single bond is shown as a dash, unless a broken line, a wedge or a wavy line is used to depict stereochemistry,[1] a carbon-

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

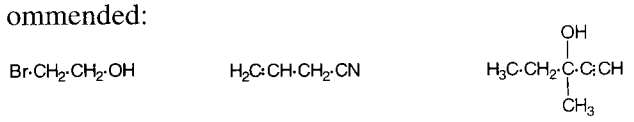


2.2 In computer-aided drawing, because it takes time to insert dashes, a single bonding dash between the atoms of an aliphatic chain need not be used. Nevertheless, in this compact form:

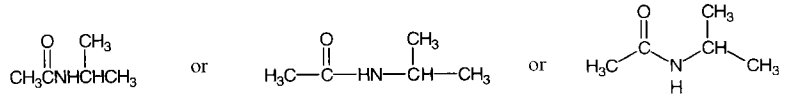
- a dash is used to show a single bond between a substituent and a chain or between a chain and a ring;
- a double dash and a triple dash are used to show a double bond and a triple bond respectively;
- dashes, broken lines or wedges are used to depict stereochemistry.[1]



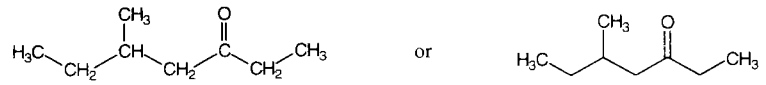
Sometimes dashes are replaced by dots, but this practice is not recommended:



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:

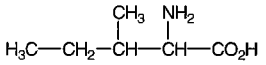


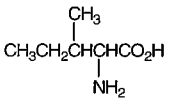
This form of representation is particularly useful for drawing long carbon chains and is often used in chemical literature. Moreover, this is the form that computer drawing programs are designed to use.

[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.

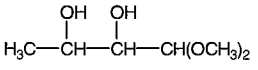
2.4 The groups at the left-hand end of the formula are always inverted, except in the compact form without dashes.

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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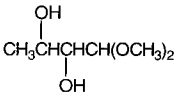
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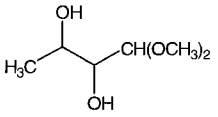

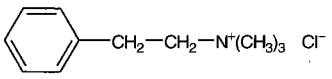
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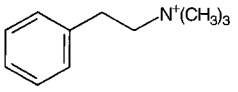
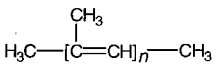


$[(H_3CO)_2CH]_2NH$ $(HO—CH_2—CH_2)_3N$ or $(HOCH_2CH_2)_3N$

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).

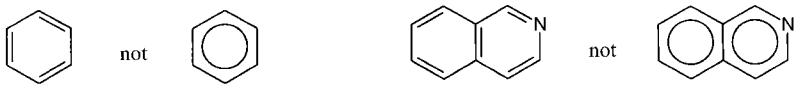
2.8 In a polymethylene chain, when one extremity is linked to a heteroatom, the methylene group linked to that heteroatom may be left outside the brackets if a contracted group such as hydroxymethyl, aminomethyl, etc., is to be shown:

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

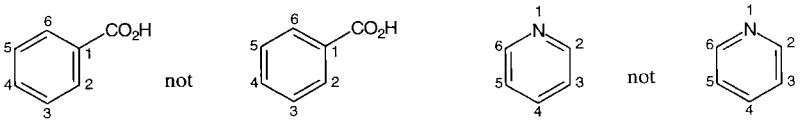
3. Cyclic structures

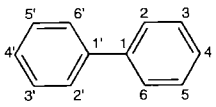
3.1 Rings are shown in full as polygons. The symbols of the carbon atoms that form the ring are not shown, but are represented by the vertices of the rings. The hydrogen atoms attached to them are not represented unless they are needed to show stereochemistry. The symbols of atoms other than carbon are 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):



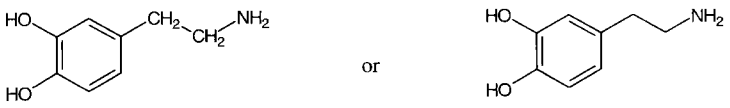
In monocyclic aromatic compounds, double bonds should be arranged to have the lowest possible numbering:



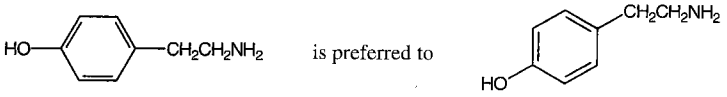


3.3 In fused polycyclic systems a double bond should form the fusion bond nearest to the right-hand side:

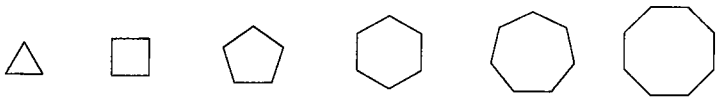
3.4 Six-membered rings should be represented with a vertex at the base rather than a horizontal bond when the chains linked to them are represented in the form of lines at an angle to one another (as is preferred for acyclic chains – see section 2.3):



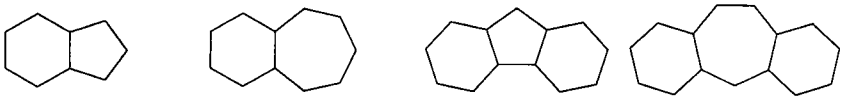
3.5 Depiction of the ring with a horizontal bond at the base is, however, preferred when the chains are shown in the compact form:



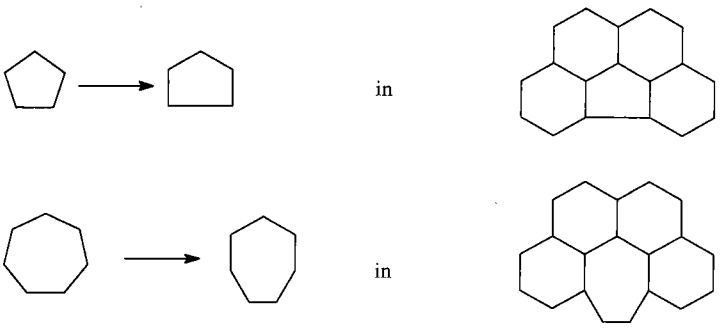
3.6 Rings are shown as regular polygons when they consist of up to eight atoms:



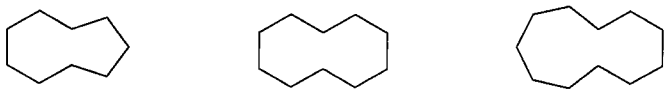
3.7 Wherever possible, the regularity of the polygons is maintained in the drawing of fused cyclic compounds:



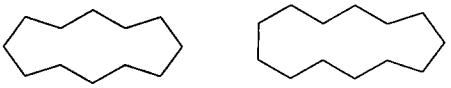
3.8 However, in fused polycyclic systems the polygons may often be distorted in order to maintain the symmetry of the structure:



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:

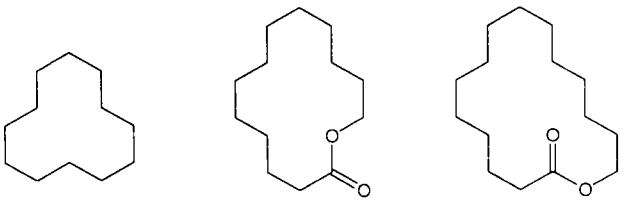


9 10 11



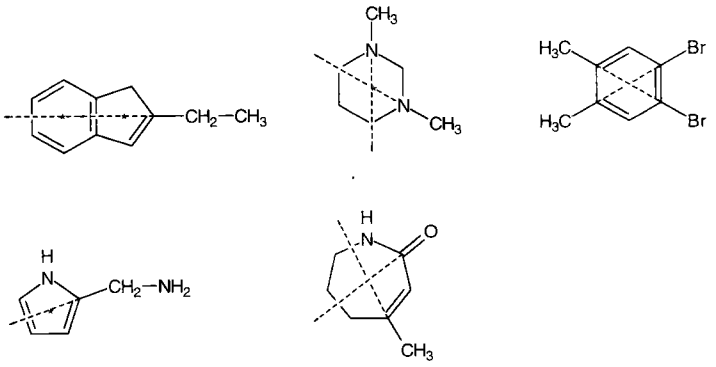
12 13

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:

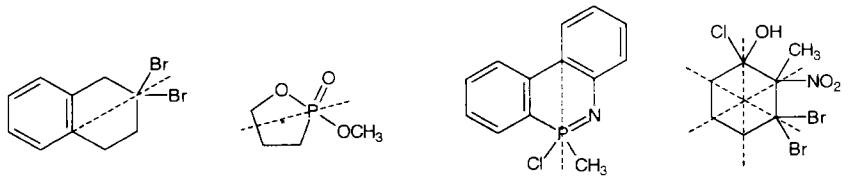


12 14 16

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:

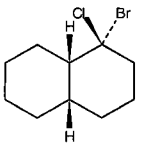


3.12 Where two substituents are attached to the same ring atom, they should generally both be at the same angle to the bisector, and preferably at a right angle to the adjacent side:

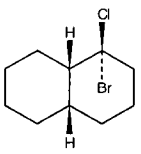


However, for the graphic representation of certain structures, such as steroids, other considerations may have priority.

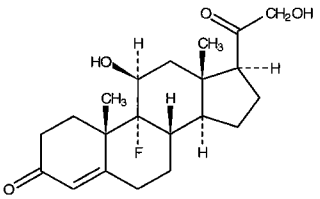
3.13 Substituents are normally placed outside rings, except in steroids, terpenes and alkaloids (see sections 9, 10 and 12) and where substituents attached at bridgeheads can only be displayed inside the rings of polycyclic structures:



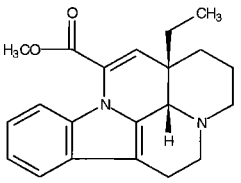
not



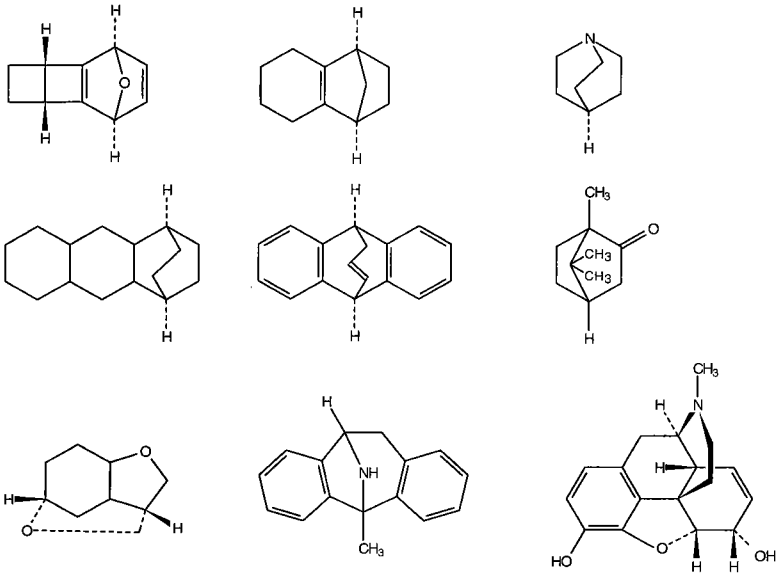
but



or

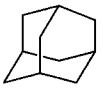


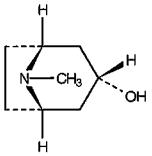
3.14 In bridged structures, a non-atomic bridge (direct bond) is represented by a straight line, an atomic bridge by lines at an angle to one another. The symbols for carbon atoms are not shown; however, if the bridge contains one or more heteroatoms, the atomic symbols for those atoms are shown. To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



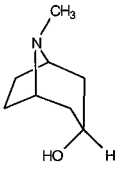
3.15 Sometimes a three-dimensional approach is possible, if a planar representation is considered not clear enough:

or





or



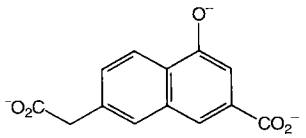
4. Ionic structures

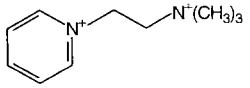
4.1 In general, in ionic structures, the cationic part is placed on the left and the anionic part on the right.

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.

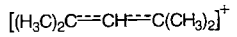
4.3 A terminal charge is shown as a superscript on the right of the group concerned, unless the order of atomic symbols in the group is reversed, when the charge is shown as a superscript on the left. In a lateral acyclic chain, if there is no space for a superscript on the right of the atom concerned, 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:

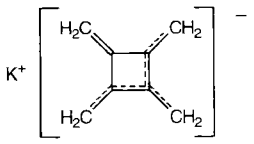
Na^+ Al^{3+} Cl^- SO_4^{2-}

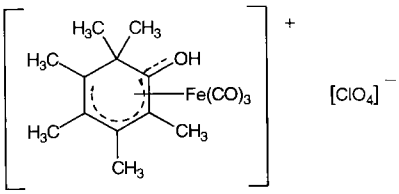




4.4 In structures with delocalized charge, the structure is put in square brackets, with the charge sign outside them as a superscript on the right:





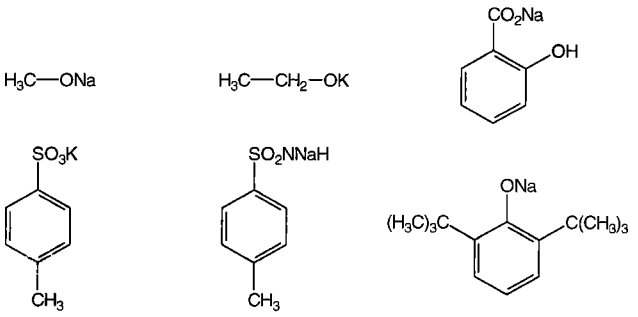


4.5 Metal salts of inorganic acids are shown without charges or bonds. If they include several metals, the symbols for the metals are shown in alphabetical order. In acid salts, the metal precedes the hydrogen. Molecules of water of crystallization or of substances of solvation follow the formula of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

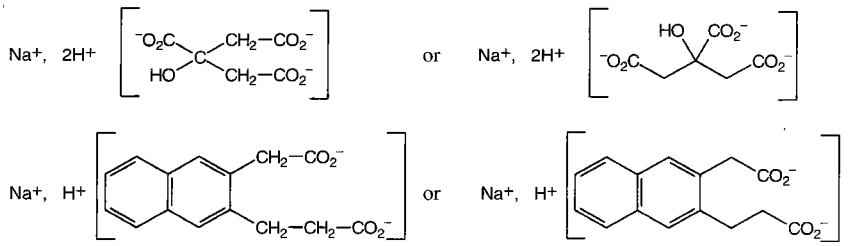
$NaBr$ $NaHCO_3$ $AlK(SO_4)_2,12H_2O$ $NaH_2PO_4,2H_2O$ $AlCl_3,4C_2H_5OH$

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:

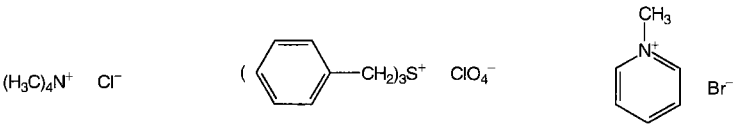


Nevertheless, ionic forms may be used when substances contain several "acid" groups to which the various cations cannot easily be attributed:



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:

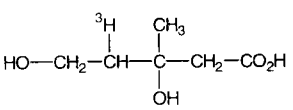


4.9 In inner salts, the positive and negative charges are shown and are normally placed in the structure as recommended above:

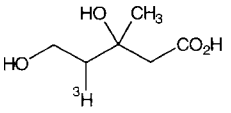
5. Isotopically modified compounds

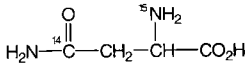
5.1 In an isotopically modified compound, the isotope used is indicated by its mass number placed as a superscript on the left of the symbol of the element concerned. Deuterium and tritium are written ^{2}H and ^{3}H respectively. The carbon atom in a ring or in a simplified angular-chain representation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

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

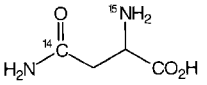


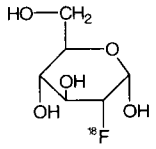
or

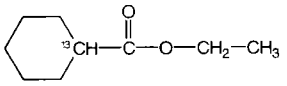




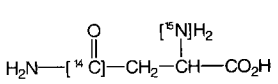
or

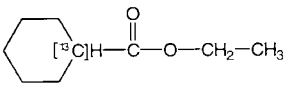






5.2 When atomic symbols in formulae are drawn without square brackets (as above) the compounds are assumed to be isotopically substituted, i.e. the atom concerned is completely replaced by the nuclide shown. To indicate isotopic labelling (partial replacement of the atom by the nuclide shown), atomic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

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

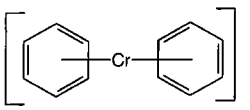
$[CoCl_2(NH_3)_4]Br$ $[Co\{SC[N(CH_3)_2]_2\}_4](NO_3)_2$ ion $[Fe(CN)_6]^{3-}$

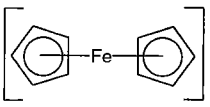
Cyclic structures

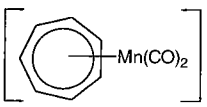
6.4 The rings follow the conventions for cyclic compounds. Where possible, the metal atom is placed in the centre of the group. Square brackets are placed round every coordination entity containing one or more rings, even if the charge is zero.

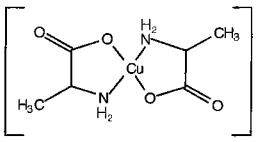
6.5 "Sandwich" structures are shown with the rings connected to the central atom by a line starting from inside the cycle and passing through one side.

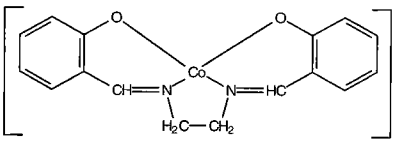
6.6 Benzene rings and condensed benzene systems in "sandwich" compounds are drawn with alternating single and double bonds. Pentagonal and heptagonal rings are shown with a circle inside:











Stereochemistry

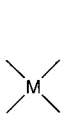
6.7 The stereochemistry of mononuclear complexes is expressed by means of special descriptors. The first of these is the "system indicator" formed from an abbreviation for the central atom geometry and the coordination number.

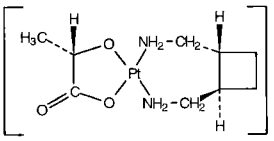
6.8 *T-4: tetrahedral complexes.* Described by the chirality symbol (*R*) or (*S*), they are shown in the same way as chiral carbon atoms, a broken line

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:

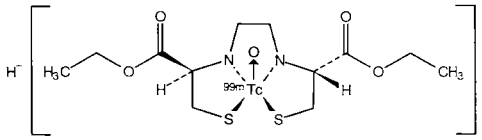




lobaplatin

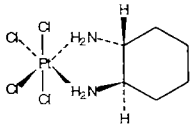
6.10 *TBPY-5: trigonal bipyramidal complexes.* The reference axis is shown in the plane of the paper; of the three other ligands, one is assumed also to be in the plane of the paper, one in front of it and the other behind it:

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

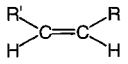
7.1 As already mentioned, a broken line denotes a bond projecting behind the plane of the paper and a filled wedge one projecting in front of that plane. A line of normal thickness denotes a bond lying in the plane of the paper. Hatched lines are sometimes used instead of broken lines. The practice of 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.

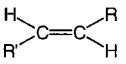
Geometric isomerism

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:

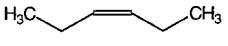


(*Z*)

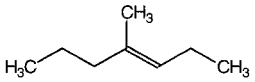


(*E*)

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):

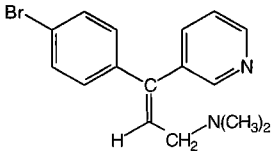


(*Z*)

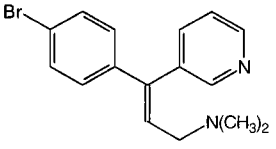


(*E*)

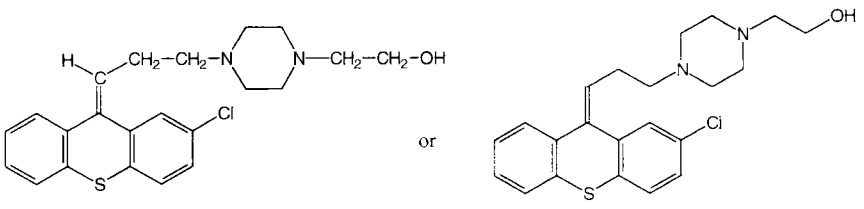
Examples of (*Z*)-compounds:



or

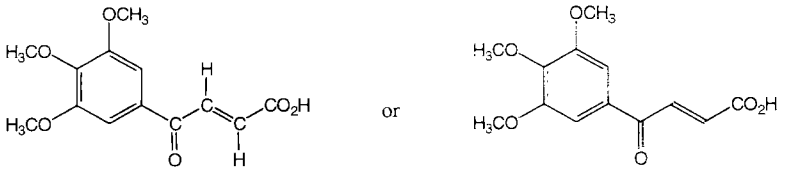


zimeldine

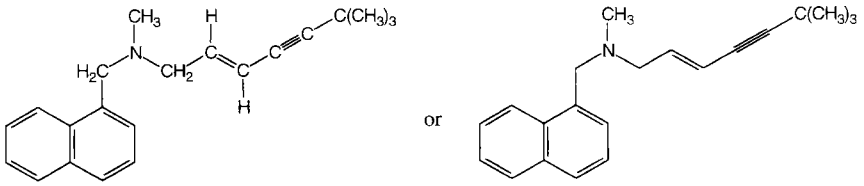


zuclopenthixol

Examples of (*E*)-compounds:



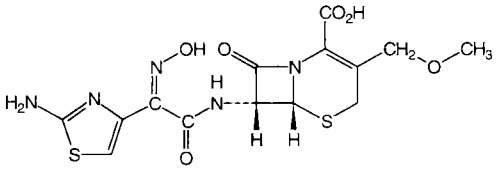
baxitozine



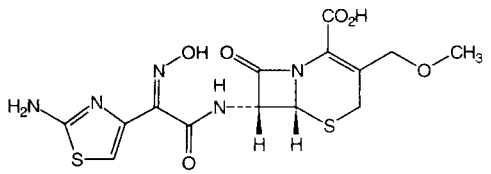
terbinafine

(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:

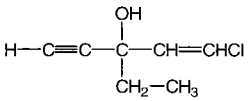


or



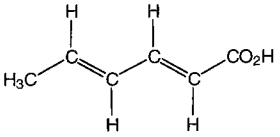
cefdaloxime (*Z*)

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

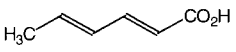


ethchlorvynol

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



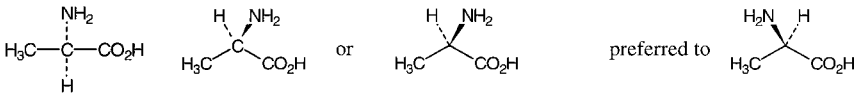
or



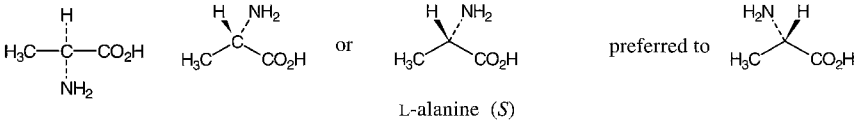
sorbic acid (*E,E*)

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).



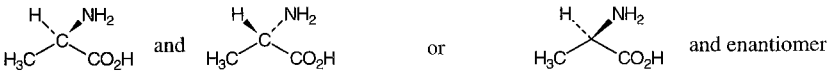
D-alanine (*R*)



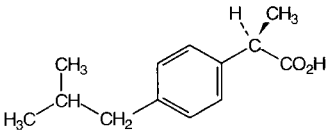
L-alanine (*S*)

(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".

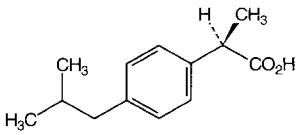


DL-alanine (*RS*)



and enantiomer

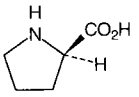
or



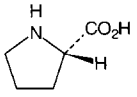
and enantiomer

ibuprofen

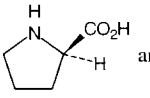
7.11 Similar representations are used for cyclic compounds with one centre of asymmetry:



D-proline (*R*)



L-proline (*S*)

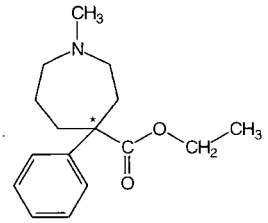


and enantiomer

DL-proline (*RS*)

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

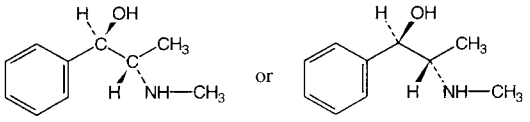
7.12 If the chirality of the centre is unknown or not specified, the bonds joining atoms or groups to the chiral atom are shown as lines of "normal" thickness. The use of a star or asterisk to identify the chiral centre may be useful:



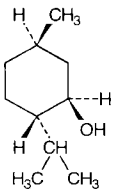
ethoheptazine (not specified)

Compounds with several chiral centres

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



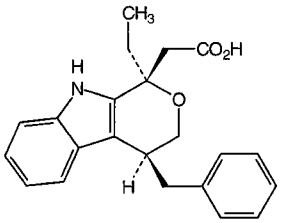
ephedrine (1*R*.2*S*)



levomenthol

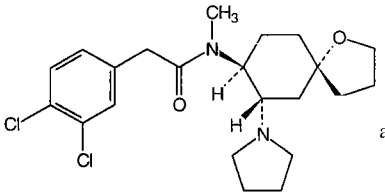
7.14 The racemates (racephedrine and racementhol respectively) are depicted by the same structures followed by the legend "and enantiomer", rather than by showing the two isomers side by side.

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



and enantiomer

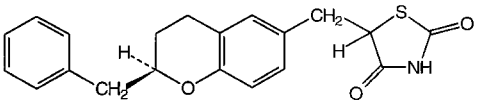
pemedolac (±)-*cis*



and enantiomer

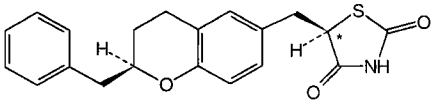
spiradoline (±)-(5*R**,7*S**,8*S**)

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



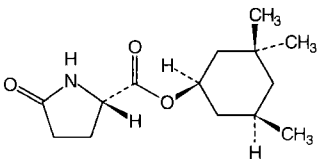
englitazone

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*":

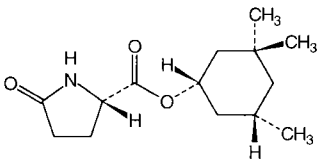


and epimer at C*

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

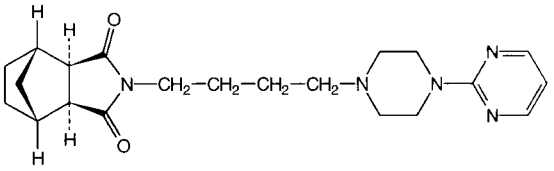


crilvastatin : (±)-*cis* only for the cyclohexane ring

Isomerism of fused rings

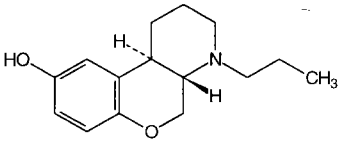
7.18 In polycyclic compounds, the atoms or groups attached at saturated bridgeheads common to two rings are shown by their symbols so as to indicate the stereochemistry resulting from the way that the cycles are fused.

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:

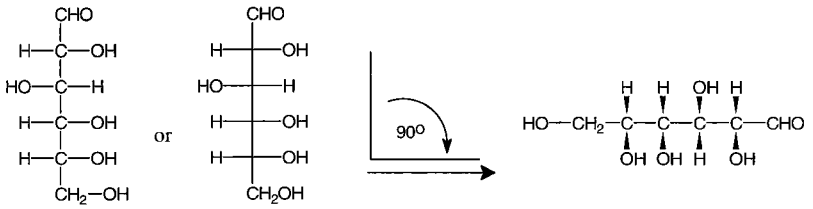


and enantiomer

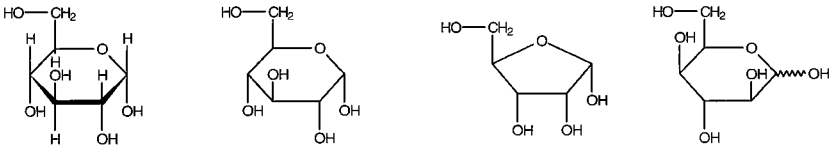
isomolpan

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:



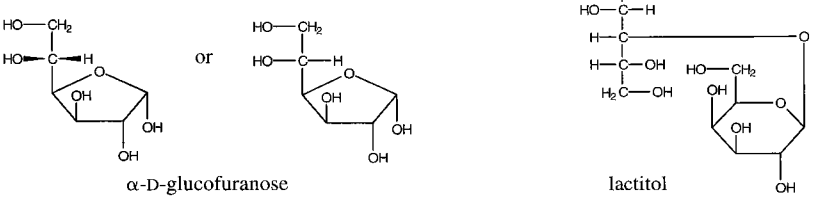
8.2 The Haworth representation is preferably used to show the cyclic forms of monosaccharides, and not those with "chair-shaped" rings. In a pyranose ring, the oxygen is in the upper right-hand corner; in a furanose ring, the oxygen is at the top in the centre. If the configuration of the anomeric carbon 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

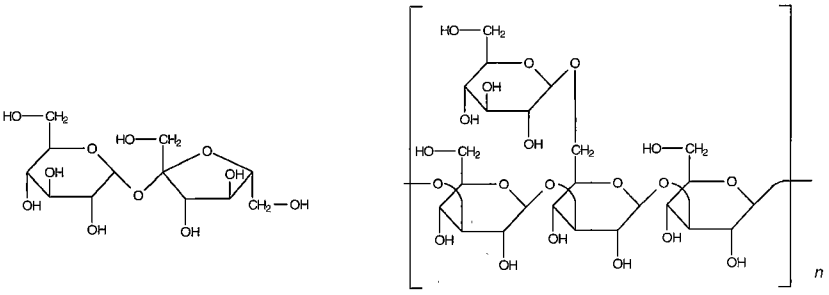
Haworth representation of α-D-glucopyranose

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



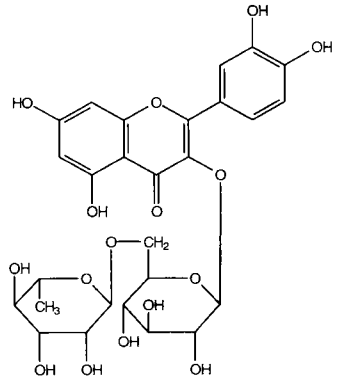
α-D-glucofuranose lactitol

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

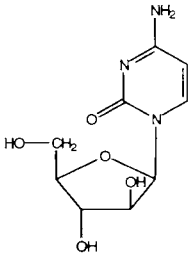


sucrose (saccharose) sizofiran

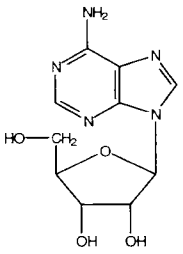
8.5 In structures that are only partly saccharide, that part is shown in accordance with the standard provisions for carbohydrates, and the rest of the structure according to the conventions for acyclic or cyclic chemical compounds, or for compounds such as steroids, polypeptides, etc.:



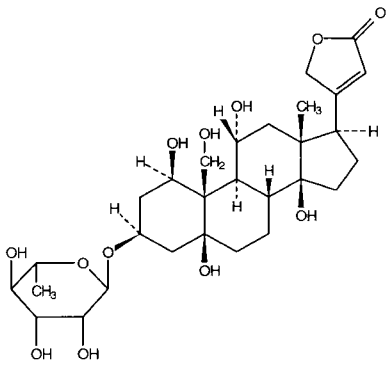
rutoside



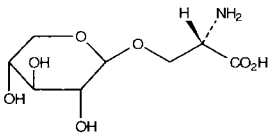
cytarabine



adenosine



ouabain



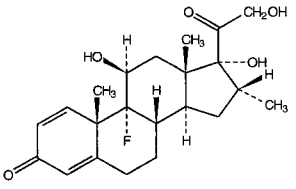
α-xylopyranosyl-L-serine

9. Steroids

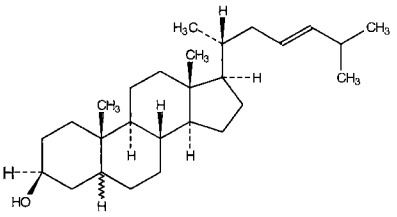
9.1 The rings of a steroid are depicted as a projection on to the plane of the paper. The projection should normally be oriented so that position 3 is at the bottom left and the regular pentagonal ring D at the top right, with position 17 uppermost.

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.

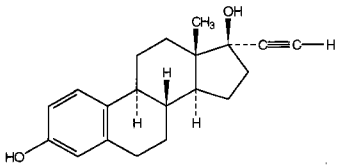
9.3 The backbone of a side-chain at C-17 is best shown as in the plane of the paper (lines of ordinary thickness), the bond between C-17 and C-20 being similarly shown. Side-chains are usually represented by lines at an angle to one another, the terminal groups being set out in full, as shown below.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



dexamethasone

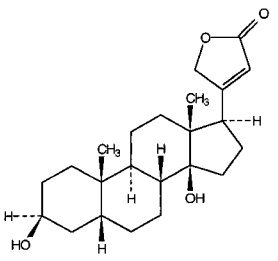


(23*E*)-5ξ-cholest-23-en-3β-ol

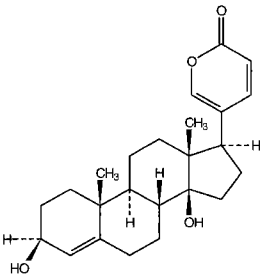


ethinylestradiol

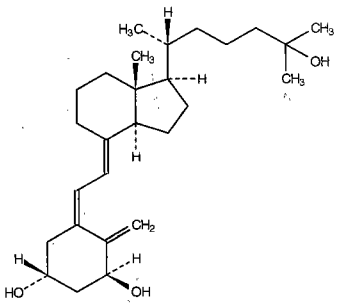
Cardanolides (see also section 8.5), bufanolides and derivatives of calciferol are depicted as shown below:



digitoxigenin



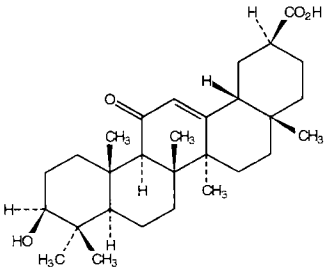
scillarenin



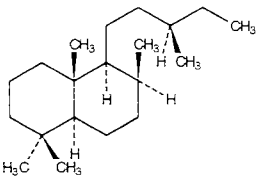
calcitriol

10. Terpenoids

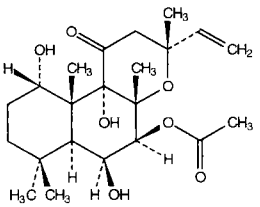
10.1 Terpenes and related compounds are depicted in a similar way to steroids, using the same conventions. Long chains are shown as lines at an angle to one another, all terminal groups being shown in full:



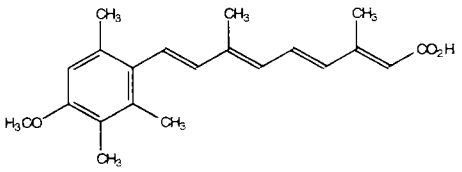
enoxolone



labdane



colforsin

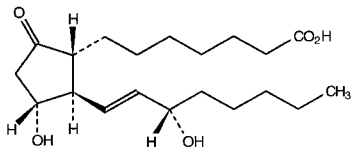


acitretin

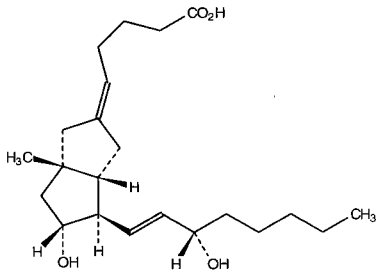
11. Prostanoids

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

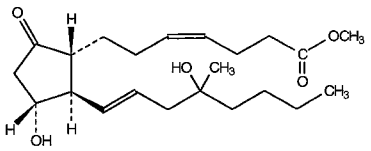
shown as lines at an angle to one another, all terminal groups being shown in full:



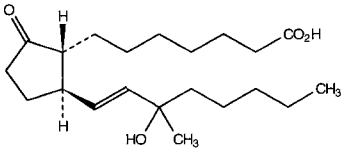
alprostadil



ciprostene

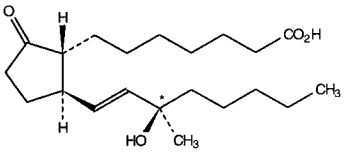


enisoprost



doxaprost

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

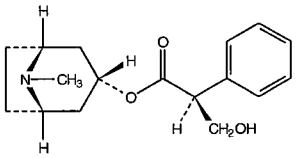


and epimer at C*

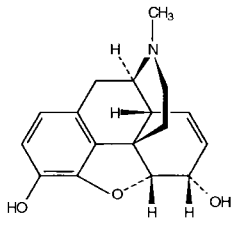
doxaprost

12. Alkaloids

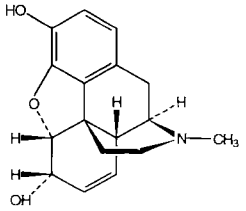
12.1 There are no general rules for depicting alkaloids, though many are depicted with a preferred conventional skeleton that can be used for a family of similar products:



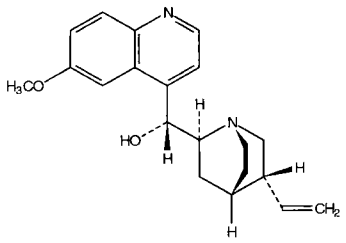
hyoscyamine



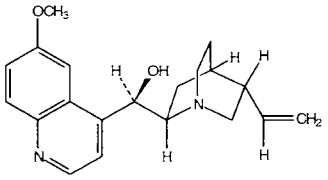
or



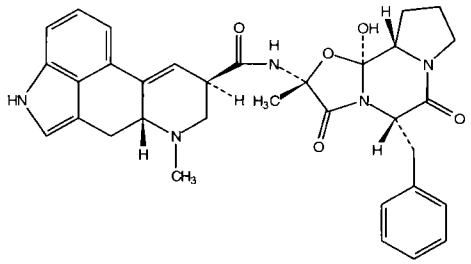
morphine



or



quinine

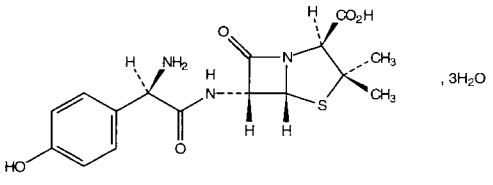


ergotamine

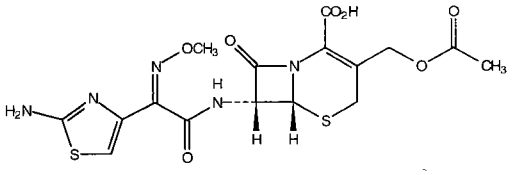
13. Antibiotics

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:

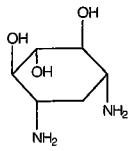


amoxicillin

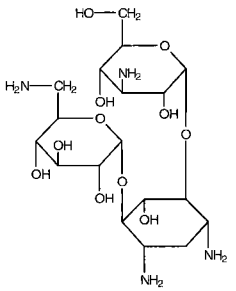


cefotaxime

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

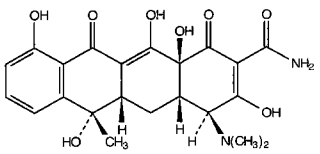


2-deoxy-D-streptamine

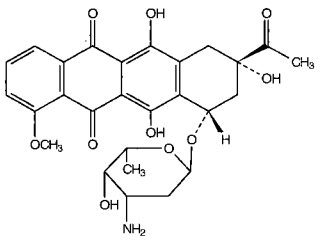


kanamycin

13.4 Tetracyclines and rubicins are depicted as follows:

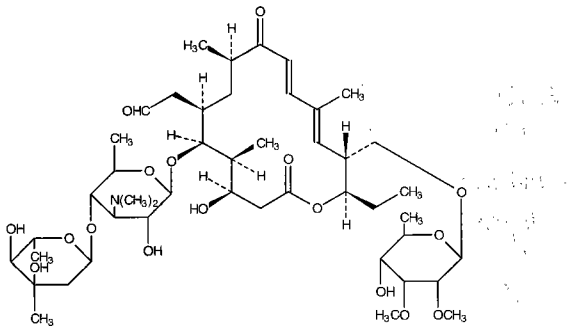


tetracycline

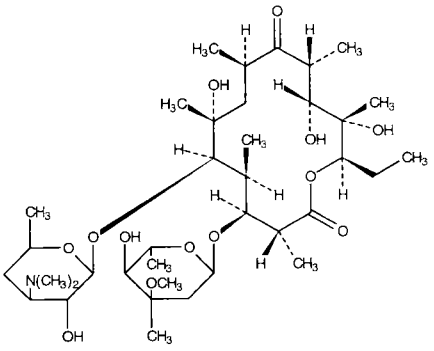


daunorubicin

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

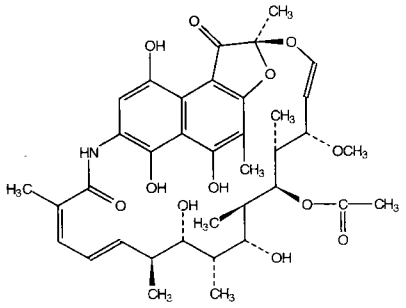


tylosin



erythromycin

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

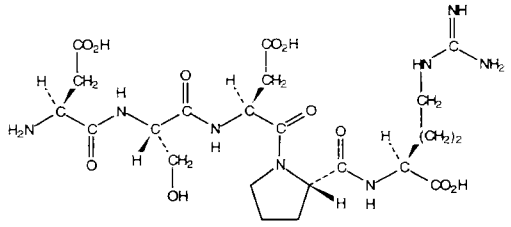


rifamycin

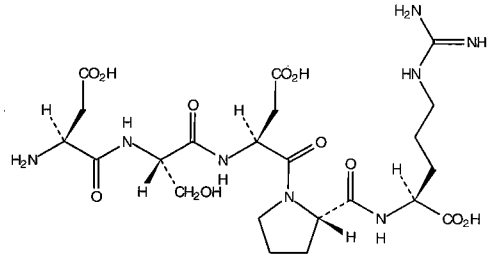
14. Polypeptides

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:



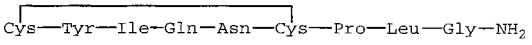
or



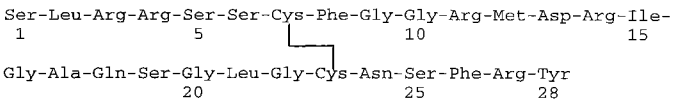
pentigetide

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.

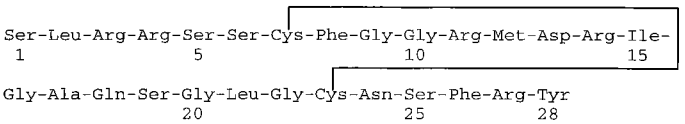
14.4 Disulfide bridges are drawn as lines attaching the S atoms to the "Cys" units but without showing those atoms. The lines must be drawn vertically and appear to pass through the letter "y". They may be placed above or below the unit chain, according to requirements. Either of the forms shown below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



oxytocin



or

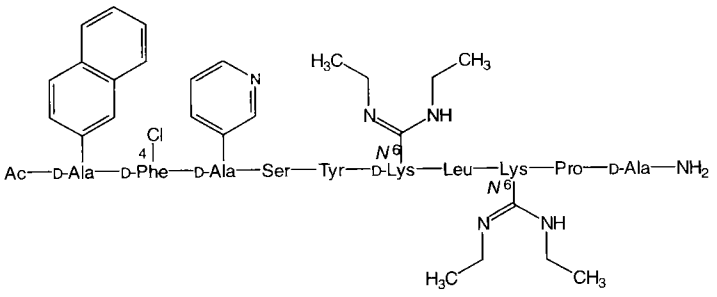


carperitide

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

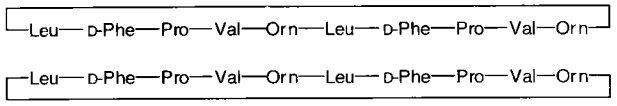
14.5 If an amino acid residue is substituted on the N-2 atom, the symbol for the substituent is placed before the three-letter code. If a side-chain modification occurs, the substituent may be depicted either in full or by

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:

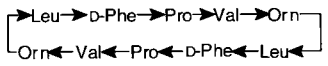


ganirelix

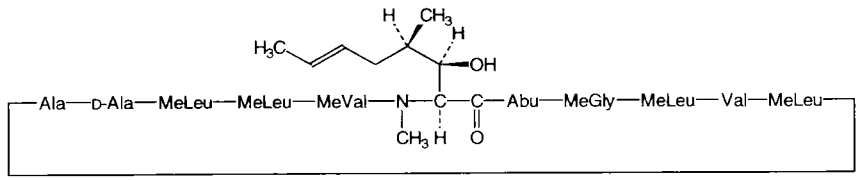
14.6 In cyclic peptides, the amino acid sequence is formulated in the usual manner but the residues at each end of the line are joined by a lengthened bond. If the residues are written on two lines, the sequence is reversed on one of them; hence the CO to NH direction within the peptide bond must be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



or

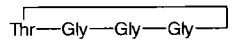


gramicidin S

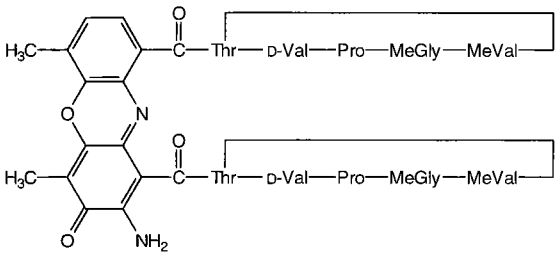


ciclosporin

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:

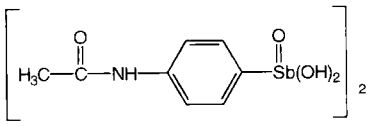
```
APPRLICDSR  VLERYLLEAK  EAENITTGCA  EHCSLNENIT  VPDTKVNPYA

WRKMEVGQQA  VEVWQGLALL  SEAVLRGQAL  LVNSSQPWEP  LQLHVNKAVS

GLRSLTTLLR  ALGAQKEAIS  PPNAASAAPL  RTITADTFRK  LFRVYSNFLR

GKLKLYTGEA  CRTGD
```

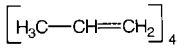
15. Polymers

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.

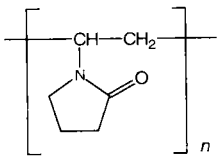
15.2 Repeated groups are either "monomers", i.e. "normal" structural formulae, or "repeated structural units", which are relatively complex multivalent radicals.

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:

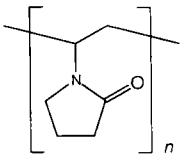




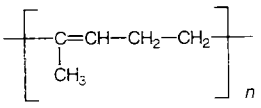
15.4 By and large, polymers are depicted as repeated structural units in which terminal bonds are shown. In linear polymers, such units are bivalent radicals:



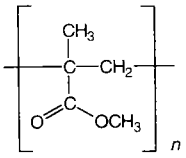
or



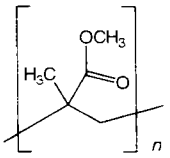
polyvidone



polyisoprene

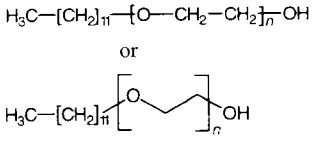


or

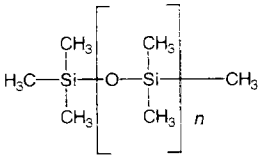


poly(methyl methacrylate)

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

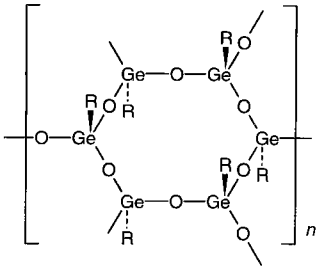


lauromacrogol



dimeticone

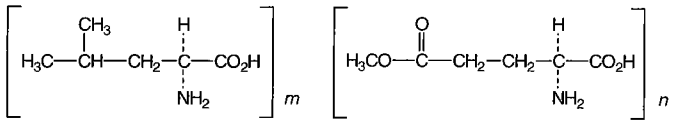
15.5 Network polymers can be shown by multivalent repeated structural units:



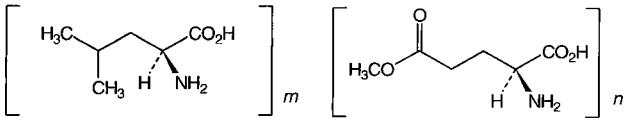
R = —CH_2—CH_2—CO_2H

repagermanium

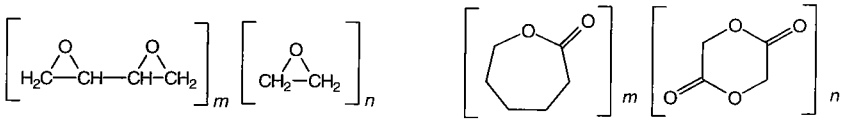
15.6 The representation of copolymers depends on what is known about the bonding of the constituent monomers. Thus normal formulae are used when it is difficult to specify the way in which the monomers are bonded:



or

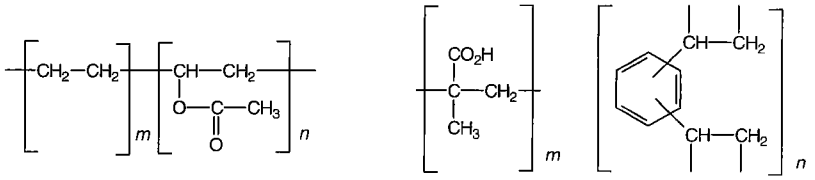


leuciglumer



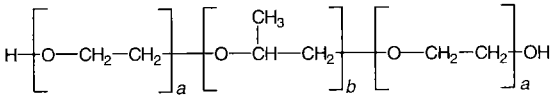
polyetadene poliglecaprone

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

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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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[1] This statement may not always be required for products intended for areas with a temperate climate.

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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..

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

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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-