WHO Expert Committee on Specifications for Pharmaceutical Preparations

Twenty-seventh Report

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WHO EXPERT COMMITTEE ON SPECIFICATIONS
FOR PHARMACEUTICAL PREPARATIONS

Geneva, 26 November – 1 December 1979

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-seventh Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 26 November to 1 December 1979. The meeting was opened on behalf of the Director-General by Dr Ch'en Wen-chieh, Assistant Director-General. He recalled that the Twenty-eighth World Health Assembly, in resolution WHA28.65, adopted the "Certification scheme on the quality of pharmaceutical products moving in international commerce" (1) proposed in the twenty-fifth report of the Expert Committee (2). He informed the Committee that the number of Member States that have agreed to participate in the scheme has grown continuously and now totals 54.

1. QUALITY ASSURANCE IN PHARMACEUTICAL SUPPLY SYSTEMS

In its twenty-sixth report (3), the WHO Expert Committee on Specifications for Pharmaceutical Preparations considered various aspects of quality assurance in pharmaceutical supply systems and suggested that to fulfil some of the objectives enumerated in resolution WHA28.66 of the Twenty-eighth World Health Assembly relating to the regulatory control of drugs, a comprehensive review of approaches to quality assurance should be recommended. A document containing such a review was considered at the present meeting; it incorporated comments by members of the Expert Panel on the International Pharmacopoeia and Pharmaceutical Preparations and by persons from other interested institutions.

A question of definition concerning the terms "drug", "medicine", "raw material", "pharmaceutical product", etc., arose early in the discussion. While there was agreement that it would not be useful in the present report to depart from the usage reflected in documents
such as the twenty-second report of the Expert Committee (4) and resolution WHA28.66, the Committee urged that steps should be taken to standardize internationally acceptable terms and definitions.

The Committee noted that the process of acquiring a pharmaceutical raw material, converting it into a finished product and making it available to the consumer involves a number of complex operations which require stringent surveillance to ensure that the user receives a satisfactory product. Moreover, these operations may involve a number of enterprises engaged in raw material production, formulation, distribution, etc., before the finished products reach those who prescribe or dispense them to the general public. A number of checks, tests and inspections must be carried out during these processes, some in the manufacturing sector, others by surveillance authorities. For divers reasons, countries have evolved a variety of procedures that they use in the quality assessment of their pharmaceutical supply systems, and yet other countries are now in the process of developing their own methods. To assist in the evolution of such national systems of drug quality assessment the Committee reviewed the document mentioned above, a revised version of which is published in Annex 1. Countries may select from this outline the features that seem appropriate to their needs.

In discussing the terms “assessment” and “assurance” the Committee came to the conclusion that the term “quality assessment” was appropriate to the activities of governmental agencies whose mandate is to assess by inspection, surveillance and other means how closely manufacturers and distributors comply with drug quality requirements. Manufacturers are regarded as fully responsible for the quality of their products and therefore the term “quality assurance” was considered more appropriate to describe their responsibilities.

Generally speaking, the Committee noted that analytical surveillance systems are directed towards finished pharmaceutical products but recognized that the quality of all raw material ingredients (including that of pharmaceutical aids) plays a crucial role in the quality of the final dosage form. The use of the term “drug quality” in the report is intended to convey consideration of all aspects of quality whatever the stage in the production process from raw material to finished product. However, whenever the context requires a clear identification of raw material or pharmaceutical product these designations are used. Because commercially available raw materials may be incorporated into a wide variety of finished products intended for administration in other than human medicine, the degree of control
over the distribution and use of such materials must be linked to their final purpose.

Countries having a quality assessment scheme, or those intending soon to put one into effect, will note the relevance and usefulness of many previous WHO initiatives concerned with aspects of drug quality and its control. The Committee strongly urged greater acceptance of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce (1) so that the quality of imported drugs can be assessed as nearly as possible on the same terms as those manufactured locally.

For a variety of reasons, drug quality specifications deemed necessary by one country may differ somewhat from those of other countries. Nevertheless, the Committee urged that, in cases where there were no persuasive reasons to the contrary, a set of generally well-accepted monographs such as those of the International Pharmacopoeia should be considered satisfactory.

The document known as “Good practices in the manufacture and quality control of drugs” (1) adopted by the Twenty-eighth World Health Assembly in resolution WHA28.66 has stood the test of time and is now widely accepted as being generally applicable to all manufacturing situations. The Committee noted that the local production of dosage forms in many developing countries is on the increase and some of the enterprises involved produce only a limited number of simple dosage forms. For such situations it would be useful to evolve from the current basic document a guideline for good manufacturing practices in such specific conditions of manufacture.

The Committee was aware of the different national legal requirements imposed in various countries on such persons as the pharmacist or the prescriber, who are involved in the final steps of the distribution of pharmaceutical products. In some countries these persons have statutory responsibilities concerning the product quality, while in others their responsibilities are governed only by professional standards. Under the first system an obligation exists to report to the drug control authority any instance of a defective product that comes to light, and the authority might wish to introduce an arrangement facilitating such reporting. Under the other system, all those who discover defective products in the course of their professional activities should be strongly encouraged to adopt the same reporting procedure.
2. REVISION OF THE
INTERNATIONAL PHARMACOPOEIA

2.1 General

In its twenty-sixth report (3), the WHO Expert Committee on Specifications for Pharmaceutical Preparations requested the Secretariat to continue the process of revising the International Pharmacopoeia on the basis of the recommendations published in its twenty-fifth report (2). In these reports the Expert Committee drew up the production schedule for the third edition of the International Pharmacopoeia, requiring a sustained effort over a number of years on the part of the collaborating experts and institutions and of the Secretariat. As a considerable delay in publication would result if the whole third edition were to appear simultaneously, it was decided to publish the edition as a set of smaller volumes based on draft texts, each volume to be issued as soon as it was completed.

2.2 Methods of drug analysis

The Committee welcomed the progress made in the publication of general methods of analysis in volume 1 of the third edition (5) and thanked the specialists and institutions concerned for their collaboration. It also noted that a number of suggestions had been received by the Secretariat from members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and interested institutions proposing the expansion of the list of methods of analysis included in the International Pharmacopoeia, especially in respect of methods used to test dosage forms, those used to test herbal drugs, and various biological methods used in the testing of pharmaceutical products. It was agreed to recommend that such methods should be elaborated for inclusion in subsequent volumes of the International Pharmacopoeia, priority being given to the methods needed to support individual monographs.

2.3 Monographs for pharmaceutical raw materials

2.3.1 Progress in the review of quality specifications

In keeping with the recommendations in the Committee's twenty-fifth report (2), the process of reviewing pharmacopoeial monographs must consist of several steps: the initial review of criteria to be used
in the monograph, followed by the preparation of drafts by the Secretariat, their subsequent review by a restricted number of specialists, and a final review in which all members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and pharmacopoeia commissions are asked to participate.

In the preparation of monographs for pharmaceutical raw materials priority was given to substances which are widely used in primary health care, guidance being obtained from the list of essential drugs established in the first report of the WHO Expert Committee on the Selection of Essential Drugs (6). As the number of active substances enumerated in that report corresponds to some 240 individual pharmaceutical raw materials (separate monographs being needed for each widely used salt or ester), it is envisaged that volumes 2 and 3 of the third edition of the International Pharmacopoeia will each include about 120 such monographs.

In accordance with the above-mentioned procedures, work was begun on the production of quality specifications for individual pharmaceutical raw materials to be included in volume 2. Draft monographs compiled by the Secretariat on the basis of criteria selected by specialists were subjected to initial review and further revised in the light of comments received by correspondence and discussed by consultants. As a result of these discussions, revised drafts of 83 monographs had been prepared and circulated to all members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and to national and regional pharmacopoeia commissions, and the first drafts of another 40 monographs to be included in volume 2 to a number of specialists for initial review. The Committee welcomed the progress made and asked the Secretariat to pursue the preparation and review of monographs for pharmaceutical raw materials.

2.3.2 International reference spectra for infrared identification tests

The identification of pharmaceutical substances by using International Reference Spectra is described as an alternative procedure in volume 1 of the third edition of the International Pharmacopoeia (5) in the section entitled "Spectrophotometry in the infrared region". The concordance between the principal absorbance maxima in the spectrum of the substance being tested with the corresponding maxima
in the relevant International Reference Spectrum is indicated as the
criterion for positive identification of the sample. The directives given
in that section pertain also to the preparation of the sample and to
checks of instrument performance. International Reference Spectra
are mentioned as alternatives to International Chemical Reference
Substances in the infrared identification tests in a number of mono-
graphs that will be included in volume 2.

The way in which International Reference Spectra might be pro-
duced was discussed. It was recommended that full-scale reproduc-
tions of suitable spectra produced from authenticated material on a
grating instrument of medium resolution power would be appropriate,
since this type of instrument might be the one most commonly en-
countered in control laboratories. The need to publish a number of
spectra of the same material produced with different types of instru-
ments was discussed by the Committee but was deemed to be un-
necessary. It was further recommended that spectra, once produced,
should be initially examined by a number of experts before publica-
tion.

Other approaches, such as the definition of a small number of the
most prominent bands in the spectrum to obviate the need for re-
producing the full spectrum, were considered by the Committee but
were thought to be inadequate for pharmacopoeial purposes.

2.3.3 Clarity of solutions

In a number of draft monographs a test for “clarity of solution”
has been introduced, without, however, any relevant standard of
clarity having been defined. This question has been taken up in recent
revisions of several pharmacopoeias and a proposal along similar
lines has been considered for the International Pharmacopoeia: a
clear solution will be defined as being less opalescent than a very
slight standard opalescence obtained in the reaction of methenamine
with hydrazine. From the analytical point of view, the slight opales-
ence thus defined is thought to be a considerable advance on the
standard opalescences derived from silver chloride or barium sulfate.

The Committee welcomed this approach. It recommended also that
further studies should be carried out on the definition of solutions of
greater opacity that may be used in situations when some degree of
opacity is permitted in a specific test.
2.3.4 Colourless solutions

In a number of draft monographs a requirement has been introduced that the solution of the substance should be colourless, without the relevant standard having been defined. It has been considered that a definition of a colourless solution may be proposed in terms of standard colour solutions described in volume 1 of the third edition of the International Pharmacopoeia (5) in the section entitled "Colour of liquids". The lowest dilutions of the standard colour solutions Bn0, Gn0, Rd0, and Yw0 will be used, the matching being made with the standard colour solution of most appropriate hue. The Committee endorsed the proposal.

2.3.5 Safety tests for some antibiotics

In the process of commenting on draft monographs several members of the Expert Advisory Panel indicated that the dose levels for pyrogen tests and tests for undue toxicity on several antibiotics used for parenteral administration proposed for the third edition of the International Pharmacopoeia and based on those that were prescribed in the second edition (7) do not reflect the progress achieved in the technology of manufacture of these substances. In several national pharmacopoeias the dose levels used for these tests are several times higher.

The Committee considered that a general increase of the dose levels used in these tests seems appropriate, but that further opinions should be requested from the members of the Expert Advisory Panel and other specialists.

2.3.6 Use of the Limulus amoebocyte lysate test

In connexion with the discussions referred to in section 2.3.5, the Committee noted that the use by drug quality control laboratories of the Limulus amoebocyte lysate procedure in testing for the absence of bacterial endotoxins is expanding, and that in the process of the revision of the International Pharmacopoeia the Secretariat should investigate the possibility of applying this type of test for pharmacopoeial purposes. The Committee also noted the position expressed on this subject in the thirtieth report of the WHO Expert Committee on Biological Standardization (8).
2.3.7 Stability information in monographs

Comments on the format of monographs for the International Pharmacopoeia included a proposal to give information concerning the lack of stability of pharmaceutical substances that are easily degraded in adverse storage conditions such as occur in tropical climates. Information of this kind may be based on data obtained in recent studies on the stability of a number of substances (9).

The Committee considered that such statements could be incorporated as additional information in relevant monographs. An appropriate statement should also be included in the general notices concerning the possible adverse effects of light, even on substances which are stable in adverse conditions of temperature and humidity.

The Committee also expressed its hope that the stability studies mentioned above will be extended to cover all the pharmaceutical substances to be included in volumes 2 and 3 of the International Pharmacopoeia.

2.4 Monographs for dosage forms

It was noted that the second report of the WHO Expert Committee on the Selection of Essential Drugs (10) contains not only the names of the drug substances considered essential for primary health care but also a number of dosage forms derived from them. The publication of volume 3 of the third edition of the International Pharmacopoeia should virtually complete the collection of specifications for pharmaceutical raw materials, and it seemed appropriate to the Committee that attention should next be turned to the provision of specifications for the most important dosage forms of those substances. Before this could be begun general consideration would have to be given to quality requirements for dosage forms—notably injectable preparations—other than the solid oral dosage forms, which had already been treated, and proposed formats for monographs on various dosage forms should be prepared.

2.5 Monographs for pharmaceutical aids

The Committee recommended that consideration should be given to assessing the possible need for preparing monographs for the most widely used pharmaceutical aids—i.e., materials such as excipients, antioxidants, and colorants—that, although not themselves clinically
active, were necessary to produce an acceptable dosage form. Such assessment might be combined with the establishment, on a worldwide basis, of a list of pharmaceutical aids that, because of their widespread usage, merited priority attention.

3. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES FOR PHARMACEUTICALS

3.1 Reports from the WHO Collaborating Centre

Reports from the WHO Collaborating Centre for Chemical Reference Substances were received by the Committee.

3.1.1 Establishment of new reference substances for pharmaceuticals

The Committee noted that in accordance with the authorization given in its previous reports the following new International Chemical Reference Substances had been established:

- Chlorpromazine hydrochloride
- Dicoumarol
- Ethambutol hydrochloride
- Hydrochlorothiazide
- Indometacin

- Phenoxymethylpenicillin
- Phenoxymethylpenicillin calcium
- Phenytoin
- Sulfamethoxypyridazine
- Tolbutamide

These substances are all needed in connexion with monographs proposed for inclusion in the forthcoming volumes of the third edition of the International Pharmacopoeia. It was noted that the substances had been established as tentative International Chemical Reference Substances for the time being and that a confirmatory assessment of their suitability would be made when the corresponding monographs had been finally adopted.

3.1.2 Replacement of current reference substances

The Committee also noted that replacement batches of the following International Chemical Reference Substances had been introduced:

- Chloramphenicol
- Digitoxin
- Digoxin

- Ergometrine maleate
- Estrone
- Folic acid
3.1.3 Future work

The Committee was informed that work had been initiated to replace the following International Chemical Reference Substances, since stocks were nearing depletion:

- Dexamethasone
- Etacrynic acid
- Lanatoside C
- Rose Bengal sodium

The Committee was also informed that the Centre, in its regular re-examination of the reference materials held in stock, had obtained results indicating the onset of degradation of the current International Chemical Reference Substance for Benzylpenicillin Sodium, and that further studies were being carried out to assess the need to replace this reference substance.

It was noted that about 40 additional reference substances would be required to support the specifications intended to be included in volume 2 of the third edition of the International Pharmacopoeia. The Committee was informed that the analytical examination of about 10 of these new reference substances was now nearly completed and that the Centre would make every effort to establish the remaining ones in the future in parallel with the publication schedule of the third edition.

The Committee expressed its satisfaction with the work carried out by the Centre and asked that its appreciation be conveyed to the staff of the Centre as well as to the National Corporation of Swedish Pharmacies, which sponsors the Centre’s activities.

3.2 Certificates

The Committee discussed the format of an abbreviated certificate that had been proposed for issue with the International Chemical Reference Substances instead of the full analytical reports that are at present supplied. It was recommended that the information given in the new type of certificate should be restricted to that necessary for the proper use of the reference substances in connexion with the tests and assays of the International Pharmacopoeia. The full analytical reports that might be required in connexion with other legitimate uses of the International Chemical Reference Substances would, however, be obtainable from the Centre on request.
3.3 Secondary reference substances

The Committee was informed of various proposals to establish regional collections of chemical reference substances for pharmaceutical quality control, and to encourage the establishment of similar national reference materials with a view to their use on a regional basis. This might be achieved by establishing secondary reference substances, calibrated with respect to the International Chemical Reference Substances.

It was recommended that the feasibility of establishing such secondary substances should be investigated and that, if acceptable, appropriate guidelines should be developed. It was recognized that the resources available to the Centre would not permit direct participation in the task of establishing secondary reference substances but that the Centre might give considerable assistance by providing training facilities for suitably qualified personnel from regional or national laboratories.

3.4 International cooperation

The Committee welcomed the progress achieved in international cooperation between the various authorities that establish chemical reference materials and acknowledged in particular the assistance of the respective commissions of the British Pharmacopoeia, the European Pharmacopoeia and the United States Pharmacopeia in facilitating the establishment of several International Chemical Reference Substances by the exchange of materials and information.

The Committee recommended that such cooperation should be continued and extended to other institutions involved in the establishment of chemical reference materials for pharmaceuticals.

3.5 Revision of guidelines

In connexion with the discussions on various aspects of the establishment and distribution of chemical reference substances mentioned above, the Committee suggested that it might be appropriate to carry out a concurrent review of the general guidelines for the establishment, maintenance and distribution of chemical reference substances as recommended in the twenty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (2).
4. QUALITY REQUIREMENTS FOR ORAL DOSAGE FORMS

4.1 Tests for solid oral dosage forms

The Committee considered the types of tests that might be required in evaluating oral dosage forms, particularly in the context of requirements that would be suitable for inclusion in a pharmacopoeia. It was noted that in such circumstances the previous history of the dosage form being examined probably would not be available and therefore the tests applied should be designed with this limitation in mind; it was also noted that a pharmacopoeial specification should apply to the product at any time during its shelf-life. In addition, the sample available for examination might be small and the type of tests prescribed would need to take this into account.

In considering solid oral dosage forms the Committee paid attention to general requirements applicable to tablets and to capsules and suggested that other products, such as medicated powders, granules or lozenges, might need consideration in the future. The recommendations made are contained in Annex 2; certain aspects gave rise to particular discussion and these are summarized below.

It was recognized that for individual dosage forms containing small amounts of active ingredients there may be a need to control the uniformity of content. Such a control, involving the individual analysis of a number of unit dosage forms to assess possible variation, may be regarded as quite an independent test. In this case, calculation of the variation of the individual items around the mean value obtained by summing all results and dividing by the number of items examined would be appropriate. Alternatively the test may be linked to the declared content of active ingredient in the product, and the variation of each individual item from that value, rather than the mean value, may be calculated.

In the type of test based on variation about the mean value, the uniformity of the sample population is assessed irrespective of whether or not that mean value is proximate to the declared quantity. It is to be presumed that compliance with the labelled claim is adequately assessed by the assay of content. If this approach is used some slight bias in the analytical method (for example, a degree of background interference or a slightly less than quantitative extraction) may be tolerated, since the important thing is to compare the individual tablets in the sample being examined. Thus, for example, a direct ultraviolet
spectrophotometric method may often be applicable, despite a slight bias due to background, whereas it would not be appropriate if the results were to be related to the declared content. This could be of importance where manual methods are most likely to be applied.

In the type of test based on variation about the declared quantity, the method of analysis for each individual tablet must reflect the true amount present—i.e., it must be a method that is free of bias. In a manufacturing situation, where an automated method of analysis is most likely to be used, this presents little problem, since the response for the nominal or declared quantity will be set and each individual tablet assessed as a percentage deviation from it. In a small control laboratory, however, manual testing will probably be employed and problems may be encountered.

Having regard to these considerations, the Committee concluded that testing based on variation about the mean value should be recommended for general use.

In considering the application of uniformity of content requirements, the Committee was of the opinion that uncoated tablets containing less than 5 mg of active ingredient should be controlled. With sugar-coated tablets, to which a test for uniformity of weight would not be applicable, it was felt desirable to increase the scope of application of the test for uniformity of content to include tablets containing 10 mg or less.

Another aspect of testing for uniformity (whether of overall weight or content) of unit dosage forms was also discussed. The recommendations made in Annex 2 concerning uniformity of weight assessments are based on the long-established and widely used determination by attributes. A proposal that this should be replaced by an approach based on the coefficient of variation (determination by variables) was considered in depth, but it was generally felt that such a procedure was more suitable for the manufacturer's internal assessment than for an assessment to be carried out in accordance with the requirements of a pharmacopoeia. It was therefore recommended that the test by attributes, which has served well for many years, should be maintained for pharmacopoeial purposes.

In discussing the application of a test designed to assess the rate or extent of the solution of an active ingredient from the dosage form (dissolution test), the Committee noted that a multiplicity of methods and types of apparatus was available. It considered that every encouragement should be given to the selection of a restricted number of such tests to facilitate an international exchange of information. It
was also recognized that the analytical method to be used in association with such tests would usually need to be quite different from the method of choice for assaying the dosage form. The determination of the active ingredient in these circumstances (that is, dissolution in an aqueous medium at low concentration) will generally be carried out by spectrophotometry, either directly or after a preliminary chemical reaction to increase the analytical response; if this is not possible, a method should be chosen that need not be specific but is precise and has been demonstrated to be adequate in the prevailing conditions.

The application of stability-indicating tests in the testing of oral dosage forms was also discussed and it was noted that appropriate information may usually be gained by using either an assay procedure that is sufficiently specific to measure only undegraded material, or, preferably, a test for the impurities that might be expected to be formed as a result of degradation. The Committee considered that the question of stability assessments of dosage forms in general, viewed in a much wider context than was possible in a limited discussion on tests for tablets and capsules, should be recommended as an object of further study. Such a study not only should take into account the deterioration in activity (strength) of a pharmaceutical product that may occur because of degradation of the active ingredient but also should consider aspects of the physical stability of the products—for example, the development of undue coloration, the friability of tablets, the breakdown of emulsions and similar occurrences—and of the results of microbial growth.

The importance, in a limited number of cases, of a well-defined particle size of the active ingredient of a tablet was acknowledged by the Committee, but it was considered that requirements for this property could not form part of the general methods of test that were appropriate for inclusion in a pharmacopoeia. Appropriate particle size of the active ingredient in a particular dosage form can only be assured through the application of good manufacturing practices and the use of appropriate starting materials. However, some assurance that material of appropriate particle size has been used may often be obtained indirectly by measurement of the dissolution characteristics of the finished product.

In considering control procedures to be applied to enteric-coated preparations it was proposed that a pH of 6.8 should be adopted for the disintegration step of the procedure rather than one of 7.5, which is prescribed in a number of pharmacopoeias. In making this proposal the Committee was aware that some types of tablets coated with shellac
would probably be excluded by the test because of the insolubility of the coating at the lower pH value. Individual national drug control authorities may wish to take this into account when establishing respective requirements.

In connexion with the question of selection of pharmaceutical aids used in dosage forms the Committee noted that a recommendation contained in the 1971 Supplement to the International Pharmacopoeia, second edition (11), stated that any substance added in preparing dosage forms preferably should not interfere with the assays and tests in the amounts present. The Committee recommended that consideration should be given to deletion of the word "preferably".

4.2 Tests for liquid oral dosage forms

The Committee considered a preliminary document concerning general methods of test for liquid oral dosage forms and recommended that this work should be extended for discussion on a later occasion. It was noted that appropriate tests for certain categories of these liquid oral preparations (for example, hydroalcoholic products derived from natural vegetable sources) would be of importance when quality requirements for natural products were under consideration.

4.3 Guidelines for in-process control of the manufacture of some types of dosage forms

The Committee recognized that, as mentioned earlier (see section 1), manufacturing facilities for the local production of certain dosage forms are currently being established in a number of developing countries. It considered that for some types of dosage forms suitable advice should be formulated concerning in-process controls, which, though inappropriate for examination of the finished product, were nevertheless applicable and desirable at intermediate stages. Such advice might be incorporated in a guideline for good manufacturing practice in specific conditions of manufacture, as mentioned in section 1. In addition, advice on appropriate controls for particle size could be incorporated in such information, as could an extension of the concept of uniformity of weight assessment by measurement of variables, referred to in section 4.1.
5. BASIC TESTS

In its twenty-sixth report (3), the Committee discussed drug quality assurance problems arising in many developing countries owing to difficulty of access to large, well-equipped drug control laboratories. It felt that for such situations it might be useful to evolve simplified tests for establishing the identity of a drug and for ascertaining the absence of gross degradation. It recommended that the Secretariat should proceed, with the help of specialists, to elaborate such tests, priority being given in the initial stage of the programme to tests for pharmaceutical substances.

5.1 Basic tests for pharmaceutical substances

As the initial step in the establishment of basic tests, the list of pharmaceutical substances to be included in the programme was prepared, patterned after the list of monographs for pharmaceutical raw materials selected for volumes 2 and 3 of the third edition of the International Pharmacopoeia. With the help of specialists, the draft test-sheets, with simplified procedures for the confirmation of identity, were then gradually evolved for 207 pharmaceutical substances. These test-sheets included a description of the organoleptic characteristics of the substance, data on its melting point and, in many cases, on the melting point of an eutectic mixture, colour reactions, and reactions resulting in the formation of a precipitate or in fluorescence. These procedures were then subjected to verification by specialists in several drug control laboratories and laboratories of pharmaceutical schools located in countries with adverse climatic conditions. Their comments were reviewed with the help of consultants and revised procedures were produced. In the process of gradual revision special stress was put on the limitation of the number of reagents used in the procedures.

The question of the use of thin-layer chromatography was repeatedly raised in the process of preparing simplified procedures for the verification of identity, and therefore this analytical technique was specially reviewed with the help of consultants, who weighed the difficulties it involved against the advantages it offered. They considered that simple thin-layer chromatographic procedures may complete the verification of identity obtained by melting-point determination and by test-tube reactions. Such procedures should be based on the use of pre-coated plates and of an authenticated reference specimen and would require the proper selection of solvent systems that would not
easily volatilize. The detection of spots should be based either on inspection under ultraviolet light or on the action of iodine vapours.

The Committee welcomed the progress made in the elaboration of basic tests for pharmaceutical substances and asked the Secretariat to continue with the verification of the procedures, with the help of specialists involved in the project.

5.2 Simple tests for the absence of gross degradation

The elaboration of simplified procedures to confirm the absence of gross degradation of pharmaceutical substances was preceded by a laboratory study carried out by Dr. M. Pezze (9) on their decomposition in conditions of elevated temperature and in the presence of humidity, but excluding the influence of light. The presence of products of degradation was detected by various analytical techniques, mainly by thin-layer chromatography, but also by spectrophotometry or by colour reactions. In the case of substances in which signs of decomposition were found in the conditions mentioned, simple tests to detect gross degradation were evolved, using in the experiment artificially produced mixtures of which 90% consisted of intact material. In the first part of the study (9), carried out on 124 pharmaceutical substances, only 37 substances were degradable in the conditions tested; for these, simple tests of gross degradation were evolved. In a subsequent part of the study, which has recently been concluded, of 68 other substances, 26 were found to be degradable under the conditions studied.

The Committee noted the results of the study and welcomed the progress made in the establishment of simple tests for gross degradation. It recommended that at later stages of the programme the tests for gross degradation should be checked using pharmaceutical substances produced by several manufacturers. It also considered that in cases in which the products of decomposition are known to have toxic properties it would be prudent to develop simplified methods to detect small quantities of such impurities.

5.3 Basic tests for tablets and capsules

The development of simplified procedures for confirming the identity of the active substance in single dosage forms, such as tablets and capsules, should extend considerably the area of application of basic tests. The procedures might be utilized not only to confirm the identity of tablets and capsules delivered to the drug distribution system but
also to avoid the risk of a mix-up at some point during the process of manufacture, including repackaging, especially when tablets or capsules are stored or trans-shipped in bulk and only placed in their final containers at a later stage.

Technical difficulties may be encountered in the establishment of simplified procedures for the types of tablets in which the amount of excipients is large owing to a low dose of the active ingredient. The excipients customarily used are not numerous—starch, lactose, magnesium stearate, talc, etc. However, the presence of unforeseen pharmaceutical aids may give rise to analytical problems, as such materials may modify the response of the test.

When, with the help of consultants, the development of basic tests for single dosage forms is under review, it has been proposed that priority should be given to devising tests for dosage forms containing only a single active ingredient for which a basic tests procedure has already been drafted. To simplify the mode of operation, identification tests for tablets and capsules should, as far as possible, be carried out direct on a ground material or by the direct action of reagents in solution.

The Committee endorsed the proposed priorities in the work on basic tests for dosage forms. It also recommended that the work should be limited initially to identity tests, and that the approaches to testing for gross degradation of active substances in dosage forms should be subject to a separate review at a later date.

5.4 Publication of basic tests

The Committee reviewed the question of the publication of information on basic tests and recommended that it should not be linked, as previously envisaged, to the issue of the International Pharmacopoeia. Instead, such material should be published separately and should include an appropriate introduction describing the aims and limitations of the tests, as well as a detailed description of the analytical techniques employed.
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1. INTRODUCTION AND GENERAL CONSIDERATIONS

In its twenty-sixth report (1), the WHO Expert Committee on Specifications for Pharmaceutical Preparations expressed the opinion that a comprehensive review of quality assurance in pharmaceutical supply systems might be of value for national programmes in the regulatory control of drugs\(^1\) and suggested that a suitable document should be prepared. The document should refer to international problems in the

\(^1\) For the purposes of this document the definition of the term “drug” is identical to that given in “Good practices in the manufacture and quality control of drugs” (2, Annex 1):

"Any substance or mixture of substances that is manufactured, sold, offered for sale, or represented for use in (1) the treatment, mitigation, prevention, or diagnosis of disease, an abnormal physical state, or the symptoms thereof in man or animal; or (2) the restoration, correction, or modification of organic functions in man or animal".
field of drug quality assurance and should include a consideration of related major WHO programmes. Since a lack of resources in certain areas might prevent the application of a comprehensive system of drug quality assurance, the Committee considered that the document should also recommend the course of action that might be taken to assure the quality of drugs being supplied under such conditions.

The present document is an attempt to provide an outline of the elements involved in the development of national programmes concerned with the regulatory control of drug quality in pharmaceutical supply systems. It is intended primarily for use by the appropriate health authorities of Member States that are establishing or expanding their national drug quality assessment system.

It is necessary for each country to develop and maintain a drug quality assessment system, which should form an integral part of a national drug control system, designed to prevent the production, export, import, and distribution of ineffective, harmful or poor-quality drugs. Such a system must be based on appropriate legislation and be supervised by a suitably qualified and properly empowered authority, supported by inspection and laboratory services. Because of the wide variations that exist in pharmaceutical supply systems the organization of quality assessment and assurance has to be adapted to meet existing conditions. The subsequent sections of this document deal with various aspects of the system in depth, where this is appropriate. The subject-matter is, however, general in nature and the suggestions contained herein can be modified to meet local needs.

In the present document the term "quality" retains the meaning given to it in the twenty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (3), which stated:

"The suitability of drugs for their intended use is determined by (a) their efficacy weighed against safety to health according to label claim or as promoted or publicized and (b) their conformity to specifications regarding identity, strength, purity, and other characteristics.

Although these two groups of factors may be considered separately, they are, to some degree, interdependent.

In order to ensure that all batches of a given drug are equally efficacious and safe, it is essential to establish adequate specifications for the drug and its dosage forms. The desired quality can then be achieved by strict adherence to these specifications. In fact, once their efficacy and safety have been established, the quality of drugs available in commerce is judged by identifying them and by determining their strength, purity, and other characteristics."

It is considered that in the assessment of the quality of imported drugs, especially in countries that are heavily dependent on pharma-
ceutical products produced abroad, an increasing role should be played by the WHO "Certification scheme on the quality of pharmaceutical products moving in international commerce" (4), and the importing countries should make greater use of it. Further details concerning the operation of the scheme are given in section 4.2.1.

It is generally accepted that the manufacturer (including the firms packaging and labelling drugs) and the distributor (including importers, wholesalers, and retail and hospital pharmacists) should be responsible for the quality of the products they manufacture or distribute. Nevertheless, this does not release other persons involved in the process of distribution of pharmaceutical products, including physicians and other health personnel, from their obligation to be vigilant and to contribute, by virtue of their experience, to the assurance of drug quality.

An important facet of quality assurance concerns the packaging and storage of drugs. Adequate specifications for containers and directions for proper packaging and storage are indispensable to prevent or diminish the loss of quality caused by handling during shipment from the manufacturer or importer, storage at ports of entry, or movement in the chain of distribution through the wholesale distribution channels to the final outlet. Inadequate packaging and storage can lead to physical deterioration and chemical decomposition, resulting in a reduction in activity and, therefore, of therapeutic efficacy, as well as the formation of possibly harmful degradation products.

The factors which concern the efficacy and safety of drugs are mentioned in this document only to the extent to which they interface with the quality notion as expressed above. Pertinent elements of pre-marketing quality assessment are discussed in some detail in section 5. A discussion of the problems of bioavailability of drugs may be found in the report of a WHO Scientific Group on the Bio-availability of Drugs: Principles and Problems (5).

Aspects such as directions for use and other information given on labels or in package inserts, including storage requirements, may have quality implications but are not discussed. The present document is primarily concerned with the quality assessment of pharmaceutical products. Additional requirements specifically applicable to biological products (such as vaccines, toxoids and antisera) are given in a number of recommendations adopted by the WHO Expert Committee on Biological Standardization or other WHO expert groups. (See, for example, the report of a WHO Expert Group on Requirements for Biological Substances: Manufacturing Establishments and Control
Laboratories... (6), and the twenty-second report of the Expert Committee on Biological Standardization, Annex 3: “Development of a national control laboratory for biological substances...” (7.)

2. ELEMENTS OF QUALITY ASSESSMENT AND ASSURANCE

The area of quality assessment and assurance includes the legal base and regulatory and technical elements.

2.1 Legal base

Drug quality assessment and assurance should have an adequate legal framework forming an integral part of general drug legislation. All regulatory and technical elements of quality assessment and assurance require the provision of legal powers to undertake these activities and to prescribe norms. The enabling legislation should provide the necessary authority to develop particular regulations in connexion with quality assurance during the manufacture, importation and distribution of pharmaceutical products and, in some cases, pharmaceutical raw materials. Additional regulations governing the practice of pharmacy, which form part of health legislation, may also be relevant here.

The responsibility for the development of guides, norms, and administrative regulations may frequently be assigned to a drug control agency. Wide differences in legal approaches exist between countries according to whether the administrative structure is centralized or decentralized. It is, however, possible in the case of a decentralized system to establish legislation that permits the sharing of responsibility and the coordination of all activities in the quality assessment of pharmaceutical supply systems.

2.2 Regulatory elements

2.2.1 General

The regulatory elements of a quality assessment system include a central administrative entity, inspection services and drug quality control laboratories.

Regulatory implementation of quality assessment requires a legal base, as mentioned in section 2.1, giving authority to a designated
agency to establish and enforce quality requirements throughout the manufacturing and distribution processes.

At the manufacturing stage, the aim is to ensure that all manufacturers, whether local or foreign, comply with good manufacturing practices. At the distribution level, the aim is to ensure that the quality of all pharmaceutical products, particularly imported items, has been properly assessed and that adequate control exists over the transport, storage and rotation of supplies, including the conditions in customs premises, warehouses, and other places in which the products are stored before reaching the final user. This also includes procedures for the recall, if necessary, of unsatisfactory products.

2.2.2 Governmental drug control agencies

To facilitate adequate national control of pharmaceutical supply systems, authority should be vested in a ministry which is responsible for health matters. This would permit the establishment of a drug control agency and the development of administrative and regulatory procedures for the control of pharmaceuticals such as drug notification, authorization or registration and for the carrying out of adequate drug quality surveillance.

Administrative and regulatory procedures based on notification, authorization or registration must provide an adequate definition or specification for each drug.

To perform drug quality surveillance, the agency needs expert staff whose training is consistent with their responsibilities. For the quality surveillance of manufacturing operations the expertise required is comparable to that described in “Good practices in the manufacture and quality control of drugs” (4).

Inspection, sampling and analysis of pharmaceutical products on the market, supplemented by information from other sources (manufacturer, distributor, other regulatory agencies and advisers, and investigations of reported defects) provides the basis for action to minimize health hazards due to poor-quality products. Study of the consolidated information provides guidance for priorities in future activities.

To perform adequately its tasks on drug quality surveillance a fully developed agency should be supported by inspection and laboratory services. Where resources are adequate, there are advantages in uniting these services in the same organization; otherwise they must be closely coordinated to maximize the efficiency of the surveillance procedures.
In countries with decentralized systems of administration the agency may be located at a central point, or it may be structured to comprise centrally coordinated regional components.

The term “agency” is capable of wide interpretation, but in the present context it is intended primarily to designate the centre of authority for drug control activities without regard to the size of the administrative organization. Alternative regulatory procedures may exist and the type and extent of control exercised will determine the resources required.

2.2.2.1 Inspection services. The inspection services act as the field arm of an agency by verifying that all elements within the pharmaceutical supply system comply with the regulations and that data submitted to the agency are factual. Verification by inspection includes assessment of manufacturing and distributing firms, as well as retail and dispensing outlets such as pharmacies and hospitals. There is scope for international cooperation in the field of inspection services, the activities of which are dealt with in more detail in section 4.

2.2.2.2 Drug quality control laboratory. A governmental drug control laboratory carries out tests and assays required to establish whether drugs conform to the specifications claimed for them. Such a laboratory may also carry out investigations on new or improved analytical methods. Its type and size will be determined by a number of factors. These include the nature of the pharmaceutical supply system, the extent of local drug production and the quantum of pharmaceutical imports, and, in addition, the availability of support from other laboratories involved in drug quality testing.

Under certain circumstances it might be useful for a group of countries to pool their efforts towards the creation of a regional control laboratory. In other circumstances, a fully established national drug control laboratory can serve neighbouring countries.

2.3 Technical elements

2.3.1 Quality specifications

Quality specifications comprise a set of properly selected standards with associated methods of analysis that may be used to assess the integrity of drugs (including dosage forms) and starting materials. Adequate specifications for a particular drug in its dosage forms for
identity, purity, strength, performance and other characteristics are necessary to assure that all batches of the drug are of uniform quality. Quality can then be achieved by strict adherence to the specifications.

In the course of drug evaluation for registration, tentative dosage form specifications are developed when clinical studies have proceeded sufficiently to suggest that the dosage form is an acceptable one. They are reviewed as further experience in drug manufacture is gained. This question was discussed in Annex 5 of the twenty-fifth report of the Expert Committee on Specifications for Pharmaceutical Preparations (2).

Quality specifications may be either public or undisclosed in nature. The public specifications are usually contained in a pharmacopoeial monograph and are stated in terms that permit objective evaluation of product quality, not only by the manufacturer but by other interested parties also.

A pharmacopoeia normally includes the general methodology of testing, monographs on pharmaceutical raw materials, including active and inactive ingredients of pharmaceutical products, and in many cases monographs on dosage forms. A number of national pharmacopoeias are kept up to date by periodic revision. Pharmacopoeias may also be issued through the joint effort of a group of countries. The European Pharmacopoeia and the Compendium Medicamentorum are recent examples of such endeavours. The International Pharmacopoeia is issued by the World Health Organization; volume 1 of the third edition (8) was published in 1979. Plurinational pharmacopoeias and the International Pharmacopoeia serve to make more uniform test methodology and specifications for a particular product.

There are many specifications that either are contained in an application for an authorization or registration or exist as the manufacturer's own specifications, which are not generally subject to public disclosure. Interested parties must therefore depend on the licensing authorities or the manufacturer for assurance that these specifications are adequate and are being met. Such assurance is mentioned in the WHO certification scheme on the quality of pharmaceutical products moving in international commerce (7) (see section 4.2.1) through its provision concerning batch certificates to be provided by the manufacturer.

Analytical criteria for judging drug quality, which relate to the identity, purity and strength of drugs and to the performance of dosage forms, the selection of such criteria for pharmacopoeial monographs and for manufacturer's specifications, and the relation between these two sets of quality requirements were reviewed in Annex 1 of the
twenty-sixth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (I).

The selection of methods and procedures used in specifications must be based on their utility for the purpose of quality assurance of pharmaceuticals, and progress in the development of new analytical tools requires a periodic review of the methodology. In establishing specifications full account must also be taken of various technical and economic constraints.

2.3.2 Basic tests

Simplified tests (basic tests) may serve in specific circumstances for verifying the identity of a drug and ascertaining the absence of gross degradation or contamination. They may be specially useful in situations in which well-equipped laboratories do not exist and in which full examination of drug quality according to procedures requiring special skills and equipment is not feasible. When a product fails the basic tests, it should not be used until its quality is established by a full analytical examination. Various aspects of the problem of the development and application of such tests are discussed in Annex 2 of the twenty-sixth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (I).

2.3.3 Requirements for good manufacturing practices

The quality of pharmaceutical products depends on the correct performance of all manufacturing operations and must be built in from the beginning of the manufacturing process. The principles for quality control procedures that should be applied to drug manufacturing practices are designated “Good practices in the manufacture and quality control of drugs” (4) (see section 2.2.2). These principles are general guides which, whenever necessary, may be adapted to meet national needs, provided the established standards of drug quality are still achieved. Manufacturing establishments with a limited product line need only utilize the relevant parts of the requirements.

The requirements for good manufacturing practice indicate that the documents relating to manufacturing procedures should contain, among other necessary information, the data concerning each starting material, as well as detailed instructions for and precautions to be taken in the manufacture of the drug. If modifications due to changes
in the equipment for processing or to the use of alternative types of ingredients are introduced, their influence on the quality, including the performance, of dosage forms has to be adequately evaluated.

3. PRE-MARKETING QUALITY ASSESSMENT

A system which serves to control the introduction of a drug to the market is a prerequisite for drug quality assessment. Quality requirements should be established by the competent health authorities (drug control agency) and these norms constitute the basis for quality assessment.

3.1 Drug notification, authorization and registration

The introduction of a drug to the market is controlled by different procedures, designated by such terms as "registration" or "licensing" in various countries. Uniform designations are given below to avoid possible confusion. The procedures thus described may be gradually evolved through discrete phases.

—A notification procedure is the least resource-intensive way of obtaining information on drugs offered for sale in a country. The amount of information requested for notification may vary. It may be initially restricted to the name of the drug and of the manufacturer, and may then be expanded to include the nonproprietary names for active substances, the composition, including inactive ingredients, and the pharmacological classification.

—An authorization procedure can be developed in which either all drugs or specified ones only require an authorization before they are marketed in the country. This procedure may vary in its stringency but it almost always incorporates the element of inspection of the manufacturer and the verification of product quality by analysis.

—A registration procedure comprises the evaluation of data intended to prove the safety and efficacy of the drug and to determine the indications for its use. The registration may include an assessment both of the drug and of the manufacturing procedures. Pharmaceutical aspects of drug evaluation for registration are described in Annex 5 of the twenty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (2). Some pertinent safety and efficacy aspects are reviewed in the report of a WHO Scientific Group on Guidelines for Evaluation of Drugs for Use in Man (9).
For products which have been used extensively and for which sufficient experience exists to demonstrate the safety of the active ingredient in similar types of preparation, the administrative requirements may be reduced to a declaration of manufacturing data and pharmaceutical quality specifications.

3.2 Drug nomenclature

The need to identify each pharmaceutical substance by a unique and universally applicable nonproprietary name has long been recognized. WHO is carrying out a programme on the standardization of drug nomenclature and has published International Nonproprietary Names (INN) for over 4000 pharmaceutical substances. Comprehensive information on the programme can be found in the twentieth report of the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances (10).

When a new drug is introduced into a country, the active ingredients should be properly identified on the label by INN or, if these are not available, by other established nonproprietary names. The names in question should also be used in all official texts.

4. DRUG QUALITY SURVEILLANCE DURING MARKETING

Quality surveillance during marketing is an integral function of a drug control agency. It is undertaken by monitoring and auditing procedures involving both inspection and laboratory testing.

The places in which drugs are manufactured, stored and distributed should be known to the control authorities. This information can be obtained by requiring all manufacturers, importers and distributors to give the control authorities official notification of their planned activities before they commence operations, and to comply with any particular regulations.

Drug quality surveillance is facilitated if lists of nonproprietary names are established for all pharmaceutical substances on the market in a country, with references to trade names where applicable.

To aid the application of procedures for the recall of pharmaceutical products, it might be useful if the control authorities had knowledge of the persons responsible for marketing in each manufacturing enter-
prise, as well as information about the distribution mechanism and the destination of the products.

4.1 Quality surveillance during manufacture

The inspection of manufacturing facilities is required to ensure that good manufacturing practices are followed at all times. In assessing manufacture, the inspector is required to pay particular attention to raw materials, manufacturing procedures, sterile operations, packaging and labelling, in-process quality control, personnel and storage facilities. Special attention should be paid to any alterations of the master formula and manufacturing procedures.

An additional mechanism of drug quality surveillance at the time of manufacture is the batch control (batch certification) of some types of drugs. According to this procedure each batch of a drug, after being declared by the manufacturer as fully conforming to quality specifications, is “put in quarantine” while a random sample is taken and analysed by a governmental drug control laboratory for confirmation of its quality. The batch is released only after a satisfactory result is obtained. Such a mechanism, which calls for a duplication of the manufacturer’s control efforts by the governmental authorities, is usually restricted to specific types of drugs, such as those that are potent but highly labile. It is usually phased out once the quality level of manufacture is considered sufficiently uniform by the drug control agency.

4.2 Quality surveillance of imported drugs

4.2.1 WHO certification scheme

The WHO certification scheme on the quality of pharmaceutical products moving in international commerce (4), when used, will provide valuable data required for pharmaceutical quality assessment of imported drugs.

The scheme permits the control authorities of importing countries to obtain information on imported drugs. In this context, it is desirable to acquire knowledge of the quality and manufacturing conditions of imported drugs similar to that which could be obtained if the product were manufactured locally. The scope of the information required may vary according to the category of the drug and the control procedure adopted in the importing country.
4.2.2 Procedures at ports of entry

At the port of entry, consignments of drugs must be stored under suitable conditions, and for as short a time as possible, to prevent deterioration. If prolonged storage is to be avoided, the proper administrative procedures must be worked out and the type of information which should accompany each shipment will have to be designated. The effective involvement of pharmaceutical officers at customs would facilitate this task.

Batch control is sometimes carried out in respect of some imported drugs and considerations similar to those mentioned in section 4.1 are pertinent here.

4.3 Quality surveillance during distribution

In the process of quality surveillance during distribution particular attention should be paid to personnel qualifications, storage facilities and transport conditions.

Every pharmaceutical product has a shelf-life during which its quality may be expected to remain within acceptable limits, but which may be seriously shortened by improper storage conditions. There is therefore a need to ensure—especially in adverse climatic conditions—that during all phases of distribution adequate conditions of storage are maintained.

For drugs that are known to have a short shelf-life, the expiry date should be stated clearly (no code being used) on all drug labels. The inclusion of expiry dates on the labelling provides a uniform system of indicating shelf-life under specified conditions of storage. In addition, the indication of the date of manufacture would further facilitate the quality surveillance of pharmaceutical products during distribution.
REFERENCES

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TESTS FOR SOLID ORAL DOSAGE FORMS

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1. INTRODUCTION

In its twenty-fourth report (1), the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended that the general monographs of the second edition of the International Pharmacopoeia dealing with solid oral dosage forms (tablets and capsules) should be revised. The report envisaged the introduction of a uniformity of content test for specific classes of tablets and some changes and improvements in the disintegration and uniformity of weight tests, for both tablets and capsules, and discussed the need for introducing dissolution requirements.

As various developments have taken place since these recommendations were made, a comprehensive review was carried out, with the help of consultants, of the whole area of quality requirements for oral dosage forms, including various types of tablets and capsules. As a result of this review, a draft text of recommendations for the most widely used solid oral dosage forms was produced.

Several general elements relating to the quality control of pharmaceuticals were specifically mentioned in the course of the review. Although they pertain equally to other types of dosage forms, it has been considered useful to state them in this introductory note to avoid possible misinterpretation of various specific recommendations discussed below.

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The recommendations given here are primarily intended for use when quality specifications of the type included in pharmacopoeial monographs are being established—that is, specifications which can be applied throughout the lifetime of the product and which are intended for the evaluation of products whose history is not necessarily known. In the case of manufacturers’ release specifications, additional criteria or more stringent standards may be applied to ensure adequate quality of the product throughout its shelf-life. Alternative methods may be used, or some of the tests in the monograph may be omitted when the manufacturer knows the identity and expected behaviour of every ingredient of the drug. A thorough discussion of these points may be found in the twenty-sixth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (2).

Similarly, the sizes of the sample to be used in the proposed tests have been selected on the assumption that the tests will primarily be used in pharmacopoeial monographs. In other cases, such as in manufacturers’ release specifications for large batches or continuous production, in the quality appraisal of very large shipments, or when a shipment is suspected of lacking homogeneity, the size of the sample may have to be selected on a different basis, taking into account statistical sampling procedures.

The review pertained mostly to pharmaceutical products containing a single active substance. In the case of pharmaceutical products containing several active substances, some modifications of the standards or of the test methods may be mandatory owing to analytical difficulties, especially in the case of criteria requiring quantitative determinations.

The question of the selection of pharmaceutical aids with regard to their intrinsic safety and the influence they may exert on the therapeutic efficacy of the dosage form was not specially reviewed, but reference was made to the pertinent recommendation published in the 1971 Supplement to the International Pharmacopoeia, second edition (3), which stated:

“Any substances added in preparing dosage forms... shall be innocuous, shall have no adverse influence on the therapeutic efficacy of the active ingredients and preferably should not interfere with the assays and tests, in the amounts present.”

Microbial contamination of oral dosage forms was discussed only briefly during the review. Certain comments on this issue appear in the twenty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (4).
The means of rapid recognition of solid oral dosage forms to prevent mix-ups and facilitate identification, such as the coding of tablets by size and shape, colour or embossment, or the coding of capsules by size, colour or print, were also briefly discussed during the review. However, the difficulties of making uniform recommendations on this important question that would be valid within the context of worldwide drug distribution were fully recognized.

2. QUALITY CRITERIA FOR TABLETS

A tablet is a compressed (occasionally moulded) solid dosage form that is formulated to contain a declared quantity of the active ingredient (or ingredients), with or without auxiliary substances. The criteria needed to assess the quality of uncoated, sugar-coated, and film-coated tablets are generally applicable also, with appropriate modifications, to other types of orally administered tablets, such as enteric-coated tablets. Other criteria may be necessary for the assessment of pharmaceutical preparations in tablet form intended for other than the oral route of administration (e.g., tablets for implantation or for the preparation of solutions).

2.1 Quality criteria for uncoated, sugar-coated, and film-coated tablets

As noted in Annex 1 of the twenty-sixth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (2), judgements concerning drug quality may be based on both objective and subjective criteria. Such attributes as the appearance, colour and odour of tablets are relevant to their integrity and quality, but they are subjective and may not be amenable to analytical measurement. The objective criteria applicable to tablets include standards, assays and tests of identity, purity, strength, and homogeneity, as well as those of performance. However, it should not be inferred that all of these types of criteria are necessarily to be applied to all tablets.

2.1.1 Standards and tests of identity

Standards and tests of identity for tablets should be designed to demonstrate unambiguously that the specimens examined contain the active ingredient (or ingredients) they purport to contain.
2.1.2 Standards and assays of the content of active ingredient(s)

The standard is expressed quantitatively as the permitted range of content of the active ingredient(s) per tablet. The assay is most frequently performed by applying an appropriate quantitative procedure to a uniformly powdered composite of several tablets, and the results of the analysis are then expressed as the content of active ingredient per tablet of average weight. However, in some instances (e.g., where grinding the tablets to powder may cause the degradation of an active ingredient, or where the nature of the ingredients makes it difficult to obtain a uniformly powdered mass) the assay has to be applied to an intact tablet or to a group of intact tablets.

The following directions are generally applicable when the assay is designed, as mentioned above, to determine the content of active ingredient per tablet of average weight:

Grind 20 tablets to a fine powder, which should be as homogeneous as possible. Use an appropriate portion of the powder to determine by an accurate method the amount of active ingredient present. The result so obtained represents the average content of the total number of tablets assayed and is used to calculate the amount of active ingredient in a tablet of average weight. The amount should fall within the acceptance limits agreed for the tablets being examined.

The acceptance limits to be assigned as the standards for a particular kind of tablet depend on the product. In the absence of justifiable reasons to the contrary, the following guidelines are recommended if the tablet contains a single active ingredient and the assay is applied to a powdered composite:

For tablets containing 100 mg or more of active ingredient: ± 5% variation from the declared content.
For tablets containing 10 mg or more but less than 100 mg of active ingredient: ± 7.5% variation from the declared content.
For tablets containing less than 10 mg of active ingredient: ± 10% variation from the declared content.

For certain classes of drugs, overages may be included, and these would obviously affect the acceptance limits to be applied.

2.1.3 Standards and tests of homogeneity

Where the assay for content of active ingredient is applied to a powdered composite, or to a group of intact tablets, information about the homogeneity of the parent population is obtained by applying either a test for uniformity of weight or a test for uniformity of content. Where the assay is applied individually to several intact tablets drawn from a parent population, these results also give an indication of whether the parent population is homogeneous.
2.1.3.1 Uniformity of weight. For uncoated tablets and film-coated tablets formulated to contain 5 mg or more of the active ingredient, the test for uniformity of weight serves to provide information about the homogeneity of a tablet population. The following procedure and guidelines are recommended:

Weigh 20 tablets and calculate the average weight. When weighed singly, the weights of no more than 2 of the tablets should deviate from the average weight by more than the deviation given below, and none should deviate by more than double the deviation indicated:

<table>
<thead>
<tr>
<th>Average weight of tablet</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg or less</td>
<td>± 10%</td>
</tr>
<tr>
<td>More than 100 mg and less than 300 mg</td>
<td>± 7.5%</td>
</tr>
<tr>
<td>300 mg and over</td>
<td>± 5%</td>
</tr>
</tbody>
</table>

If film-coated tablets fail this test it may be because of variability in the thickness (weight) of the coatings. In such a case a test for uniformity of content should be applied, and if the tablets meet the requirements of this test, they can be considered acceptable.

2.1.3.2 Homogeneity of sugar-coated tablets. The establishment of homogeneity of sugar-coated tablets may cause problems, owing to the large variability in the thickness (weight) of the coatings. It was noted that in accordance with good manufacturing practices the cores of both sugar-coated and film-coated tablets should comply with appropriate criteria for uniformity of weight before the coatings are applied. Nevertheless, this information is normally available only to the manufacturer. It was therefore recommended that sugar-coated tablets formulated to contain 10 mg or less of the active ingredient should comply with the criteria for uniformity of content. Sugar-coated tablets formulated to contain more than 10 mg of the active ingredient may be exempted from the tests for uniformity of weight and uniformity of content.

2.1.3.3 Uniformity of content. If there is a demonstrable clinical reason for precise dosage, a test for uniformity of content should be employed. In general, however, the test for uniformity of content should be applied only where the declared quantity of active ingredient in a single tablet is less than 5 mg or, in the case of sugar-coated tablets, 10 mg or less.

The following directions are considered to be generally applicable for performing the test for uniformity of content:
Individually determine the active ingredient in each of 10 tablets, using an assay of appropriate sensitivity and discrimination. Each tablet should contain an amount of active ingredient that falls within the acceptance limits agreed for the tablets being examined, except that in the case of 1 tablet the content may fall outside these limits, provided it lies within the extreme acceptance limits agreed. In the latter event a further 20 tablets drawn from the same population as the original 10 are examined; all 20 tablets so examined should fall within the acceptance limits.

The acceptance limits should be set as a permitted tolerance around the mean value of the individual determinations. It is recommended that the acceptance limits should allow a ± 15% deviation, and for the extreme acceptance limits a ± 25% deviation, around the mean value.

2.1.4 Standards and tests for impurities

Standards and tests should be introduced for potentially harmful degradation compounds that may be generated during the production and storage of the dosage form, and for contaminants whose presence may indicate a deviation from good manufacturing practices. The analytical methods and the standards depend on the nature of the impurity.

2.1.5 Standards and tests of performance

Standards and tests of performance for tablets are designed to provide some assurance that the dosage form, when administered, will release its active ingredient as it is intended to do. A suitable dissolution test should be employed as a performance test in instances in which problems may arise if the required amount of the active ingredient is not released in a reliable manner, or those in which the characteristics of the active ingredient (for example, low solubility in aqueous mixtures) may give rise to impaired bioavailability. Otherwise, the simpler disintegration test should be employed as a performance test for uncoated, film-coated, and sugar-coated tablets.

2.1.5.1 Disintegration test. There is a worldwide tendency towards the adoption of a standardized disintegration apparatus consisting of a 6-place basket-rack assembly, a suitable device for raising and lowering the assembly, and a vessel containing an immersion fluid maintained at 37±2°C. A more detailed description of this apparatus is given in Appendix 1. An apparatus of this type is described, for ex-
ample, in the United States Pharmacopeia (5), in the European Pharmacopoeia (6), and in the Pharmacopée française (7).

The following directions and criteria are generally applicable for the disintegration test for tablets intended to be swallowed:

Use 6 tablets in the test. Place 1 tablet in each of the 6 tubes of the basket, add a disc to each tube, and operate the apparatus at a constant frequency of 28–32 c/min through a distance of 5–6 cm, using water maintained at 37 ± 2°C as the immersion fluid. At the end of the time limit specified, lift the basket from the fluid and observe the material in each of the tubes: all the tablets have disintegrated completely; any residue (except fragments of insoluble coating) that remains on the screen of the test apparatus consists of a soft mass with no firm core. The time limit specified for the disintegration of uncoated tablets is 15 minutes unless otherwise indicated. The time limit specified for both sugar-coated and film-coated tablets is 45 minutes; however, if the latter fail to disintegrate when water is used as the immersion fluid, they may be acceptable if another 6 tablets drawn from the same population disintegrate completely within 45 minutes when hydrochloric acid (0.1 mol/l) is used as the immersion fluid.

2.1.5.2 Dissolution test. In general, the criterion of acceptance in a dissolution test is that a stated, substantial proportion of the declared quantity of the active ingredient will go into solution within a stated time when the tablet is subjected to standardized operating conditions. Such standardization of operating conditions for dissolution tests, including the design and proficiency of the apparatus, is indispensable if reliable reproducible results are to be obtained.

Although many types of equipment have been described for dissolution testing, the two that have been most widely used for tablets are a rotating paddle apparatus and a rotating basket apparatus. A consensus favoured the application of a paddle apparatus for general use, but also recognized the potential value of a flow-method (such as that of Langenbucher (9)) for substances of very low solubility. In all dissolution test procedures it is essential to keep to a minimum all extraneous agitation due to such sources as vibration of the motor that rotates the paddle shaft and vibration of the thermostat that regulates the temperature of the bath in which the vessel containing the dissolution fluid is immersed. Among other factors that may bias the results of dissolution tests are the presence of dissolved gases in the dissolution fluid, misalignment of the paddles or shaft, and faulty control of the speed of rotation. Calibrator tablets with known dissolution characteristics under standardized experimental conditions may be used to test the proficiency of the apparatus.

The dissolution fluid generally used is water maintained at 37°C. In some instances hydrochloric acid (0.1 mol/l), or appropriate buffers, may be employed.
The determination of the active ingredient dissolved in the aqueous medium at low concentrations may present problems that necessitate the use of a method other than the assay procedure. The method chosen need not be specific but should be of adequate precision.

2.1.6 Other considerations

The feasibility of establishing criteria for the abrasion and hardness of tablets was considered. It was noted that tests for abrasion and hardness are useful elements in manufacturer's quality control systems, and it is recommended that attempts should be made to apply such tests for pharmacopoeial purposes, at least for uncoated tablets.

2.2 Additional quality criteria for special types of tablets

Special types of tablets are used to elicit specific in vivo responses. Enteric-coated tablets may be used when the active substance is unstable in the gastric acids—e.g., erythromycin—or is irritating to the stomach—e.g., iron salts. Substances which require rapid transport to active sites or for which it is necessary to avoid a first-pass effect may be effectively administered as sublingual tablets (nitroglycerin). Slow-release tablets are used to reduce the frequency of administration or to modulate plasma drug levels by avoiding the potentially toxic peak levels that may be associated with normal tablets.

2.2.1 Enteric-coated tablets

Enteric coating is intended to prevent tablet disintegration at the low pH of the stomach fluids and allow disintegration at a higher pH to permit the release of the active substance in the intestine.

2.2.1.1 General considerations. The selection of methods and standards to assure identity, content of active ingredient and purity of enteric-coated tablets is done according to general considerations recommended for tablets (section 2.1). The selection of acceptance limits for content should be based on the recommendations given in section 2.1.2, taking into consideration both the analytical factors involved (potential excipient and coating interference, and the limitations of the assay method) as well as the production factors (application of good manufacturing practices). Special considerations are
required in respect of standards for disintegration, or dissolution when specially needed, and sometimes in respect of uniformity of content.

Inter-tablet variation in coating thickness makes weight variation tests unreliable as indicators of homogeneity in enteric-coated tablets. It may be necessary, therefore, to introduce uniformity content tests for enteric-coated tablets with a declared content of active ingredient in a single tablet higher than the amounts indicated in section 2.1.3.3.

2.2.1.2 Disintegration test. When subjected to a disintegration test enteric-coated tablets should resist the action of acid at pH 1.2 (acid integrity step of the procedure) but should disintegrate at pH 6.8 (disintegration step of the procedure). The test requires that the tablet and its coating should show no sign of rupture after exposure to an acid medium for a specified time and that disintegration should occur within a specified time in the simulated intestinal fluid.

The following modifications of the conditions described in section 2.1.5.1 are recommended for enteric-coated tablets. The test is carried out with 6 tablets. Hydrochloric acid (0.1 mol/l) is used for the acid integrity step of the procedure. It is then replaced by a phosphate buffer of pH 6.8 for the disintegration step (no enzymes need to be added to the liquids in either step); the temperature of both liquids is maintained at 37 ± 2 °C. The tablets remain intact in the acid medium for 120 minutes and disintegrate completely within 60 minutes in the phosphate buffer, except for fragments of insoluble coating, which may remain on the screen.

It has been suggested that a test should be introduced for the dissolved active substance in the acid integrity step of the procedure to detect the diffusion of the active substance through the coating itself or through minute pores in it. This additional test should not be done routinely but only when diffusion is suspected from other evidence.

2.2.2 Sublingual tablets

The active ingredient in tablets inserted beneath the tongue is absorbed directly through the oral mucosa. Drugs for sublingual administration are intended to provide prompt relief for acute conditions, thus obviating the need for parenteral administration by professional health workers. The dosage form should be fabricated in such a way that the active ingredient is rapidly released into the sublingual fluids. The time limit for a disintegration test should be 5 minutes.
2.2.3 Slow release oral dosage forms

Preparations designed to permit longer dosage intervals of short-acting drugs, to prevent gastric irritation, or to provide a more even drug plasma concentration profile than is possible with normal tablets are generally known as slow release preparations. They have also been designated controlled release, depot, gradual release, prolonged release, retard, delayed action and extended action dosage forms. Their components, which usually have different release rates, are encapsulated, compressed or moulded into tablets. When in the appropriate part of the gastrointestinal tract, each component is expected to release the active ingredient or ingredients at such a rate as to achieve the desired effect.

The benefits of these formulations may be offset by variable absorption or too rapid delivery of the active substance due either to variations in physiology or to faulty production.

2.2.3.1 General considerations. The requirements regarding identity, content of active ingredient and limits of impurity of slow release tablets are similar to those for tablets in general. While manufacturers are able to control and test the content of the various dosage form components required to achieve different timed release patterns, the pharmacopoeial requirements may only specify limits for the total drug content of the finished product. The analytical method should take into account the possibility that the extraction of a drug from slow release formulations may not be straightforward.

Disintegration tests are usually not required for slow release preparations.

2.2.3.2 Dissolution criteria. The efficacy of the preparation will depend on the in vivo drug release characteristics and on the dosage form’s containing the correct amount of drug in each timed release component. Dissolution standards should normally be part of the manufacturer’s quality control specifications and these should be developed with a knowledge of the particular plasma level characteristics of the specific formulation.

Criteria suitable as pharmacopoeial requirements should specify upper and lower limits for the amount of drug dissolved in a fluid of appropriate pH after specified times—for example, after 1 hour and after 5–7 hours. The modification of the pH of the test fluid may be desirable for some slow release oral dosage forms. The test procedure
should be so designed that the amount dissolved at the completion of the test should be equivalent to at least 75% of the declared drug content.

The apparatus chosen should permit adequate fluid agitation, the removal of samples, an isothermal environment and a suitable alteration of pH if needed.

2.2.4 Effervescent tablets

Effervescent tablets are uncoated tablets intended to be dissolved or dispersed in water prior to oral administration.

An additional test for an effervescent tablet involves placing it in a vessel containing a suitable volume of water at ambient temperature and observing the disintegration accompanied by effervescence, after which the small particles are dissolved or dispersed in the water. The time to dissolve or disperse should be quite short (about 2 or 3 minutes).

3. QUALITY CRITERIA FOR CAPSULES

A capsule is a solid dosage form consisting of a drug enclosed in a shell. The shell has a gelatin basis and is designed to liberate its contents after ingestion. Both hard and soft gelatin capsules exist. The discussion below pertains to gelatin capsules intended for oral use only. Capsules of which the shells are not swallowed but which have to be opened and emptied before their contents are ingested, capsules for rectal and vaginal application, and empty gelatin capsules were excluded from consideration, as were all capsules with shells consisting of materials other than gelatin (e.g., starch and synthetic polymers).

Hard gelatin capsules are composed of two joined parts, the body and the cap. During the filling operation the two parts are separated and powders or granules, etc., are placed in the body. When the capsule is closed after replacement of the cap it may be sealed by some suitable means.

The shell of soft gelatin capsules is in one piece and is somewhat thicker than that of hard gelatin capsules.

The content of the capsules consists of one or more active ingredients, which may be mixed with suitable diluents and other additives.
3.1 Quality criteria for hard and soft gelatin capsules

General considerations concerning the use of both objective and subjective criteria for arriving at a judgement on the quality of tablets as set forth in section 2.1 apply equally to capsules.

A special requirement for capsules is that they must be firmly closed and that their surface must be clean and free from traces of their contents. If the capsules have a foreign odour, this may be caused by mould growth on the gelatin shell. In testing for foreign odour the capsules should first be exposed to the open air for 15 minutes.

3.1.1 Standards and tests of identity

Standards and tests of identity for capsules should be designed to demonstrate unambiguously that the samples examined contain the active ingredient (or ingredients) they purport to contain.

3.1.2 Standards and assays of content of active ingredient

The standard is expressed quantitatively as the permitted range of content of the active ingredient(s) per capsule. The assay is most frequently performed by applying an appropriate quantitative procedure to a uniformly mixed composite of the content of several capsules, and the results of the analysis are then expressed as the content of active ingredient per capsule of average weight. The result so obtained represents the average content of the total number of capsules assayed and is used to calculate the amount of active ingredient in a capsule of average weight. However, in some instances (e.g., where the shell may have absorbed part of the active ingredient) the assay has to be applied to an intact capsule or group of intact capsules.

The acceptance limits to be assigned as the standards for a particular kind of capsule depend on the product. In the absence of justifiable reasons to the contrary, the following guidelines are recommended where the capsule contains a single active ingredient and the assay is applied to a mixed composite of the content of 20 capsules:

For capsules containing 100 mg or more of active ingredient: ± 5% variation from the declared content.

For capsules containing 10 mg or more but less than 100 mg of active ingredient: ± 7.5% variation from the declared content.

For capsules containing less than 10 mg of active ingredient: ± 10% variation from the declared content.
For certain classes of drugs, overages may be included, and these would obviously affect the acceptance limits to be applied.

3.1.3 Standards and tests of homogeneity

Where the assay is applied to a group of intact capsules, or to a mixed composite of their content, information about the homogeneity of the parent population is obtained by applying either a test for uniformity of weight or a test for uniformity of content. Where the assay is applied individually to several intact capsules drawn from a parent population, these results indicate whether the parent population is homogeneous.

3.1.3.1 Uniformity of weight. For capsules formulated to contain more than 10 mg of the active ingredient the test for uniformity of weight serves to provide information about the homogeneity of a capsule population. The following procedures and guidelines are recommended:

Weigh 20 intact capsules individually, and calculate the average weight. The weight of each capsule should be within 90–110% of the average weight.

If not all the capsules fall within the aforementioned limits, weigh the 20 capsules individually, taking care to preserve the identity of each capsule, and remove the contents as completely as possible. For soft gelatin capsules, wash the shell with ether or some other suitable solvent and allow it to stand until the odour of the solvent is no longer perceptible. Weigh the emptied shells individually and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Determine the average net content from the sum of the individual net weights. Then determine the difference between each individual net content and the average net content. No more than 2 of the individual net weights should deviate from the average net weight by more than the deviation given below and none should deviate by more than double the deviation indicated:

<table>
<thead>
<tr>
<th>Net weight of capsule contents</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 300 mg</td>
<td>± 10%</td>
</tr>
<tr>
<td>300 mg and over</td>
<td>± 7.5%</td>
</tr>
</tbody>
</table>

3.1.3.2 Uniformity of content. If there is a demonstrable clinical reason for precise dosage, a test for uniformity of content should be employed. In general, however, this test should be applied only where the declared quantity of active ingredient in a single capsule is 10 mg or less.

The same procedures and considerations as those pertaining to tablets, given in section 2.1.3.3, are valid for capsules in respect of the test for uniformity of content and the acceptance limits to be applied.
3.1.4 Standards and tests of purity

The same considerations as those pertaining to tablets, given in section 2.1.4, are valid for capsules in respect of standards and tests of purity.

3.1.5 Standards and tests of performance

The same considerations as those pertaining to tablets, given in section 2.1.5, are valid for capsules in respect of standards and tests of performance, taking into account additional factors as mentioned below.

3.1.5.1 Disintegration test. The disintegration test for capsules gave rise to some discussion as to its usefulness. Difficulties have been observed in applying this test to certain capsule preparations, where the content of the capsules was fully liberated but where the softened contents of the capsules failed to disaggregate and pass the screen of the test apparatus. In such a case it is useful to determine the time when the shell ruptures enabling the content to emerge into the surrounding liquid medium. It became evident from the discussion that it is more difficult to propose a generally applicable procedure for the disintegration test of capsules than for that of tablets, since deviations from a general procedure may be required in specific cases. It is recommended, however, that the following directions and criteria should be followed under normal circumstances:

Use the standardized disintegration apparatus as described in Appendix 1. Use 6 capsules in the test. Place 1 capsule in each of the 6 tubes of the basket and insert into each tube, instead of a disc, a special plunger. This plunger, of which a detailed description is given in Appendix 2, is a modification of the type described in the Pharmacopoea Helvetica (9). Operate the apparatus at a constant frequency of 28–32 c/min through a distance of 5–6 cm, using water at a temperature of 37 ± 1°C as the immersion fluid. At the end of the specified time limit lift the basket from the fluid. All the capsules should have disintegrated completely and no residue, except fragments of undissolved parts of the shell, should remain on the screen of the test apparatus. The time limit for the disintegration of capsules is 30 minutes.

The use of plungers in the test decreases the size of the chamber and ensures that the capsules remain immersed without imposing any additional mechanical stress on them. If the discs described in Appendix 1 are used, the additional mechanical stress that they cause leads generally to more rapid disintegration of the capsules and reduces the discriminating power of the test. In addition, it may happen
that some capsules stick to the disc, and this may unduly prolong the disintegration time.

The narrow range of \( \pm 1 \, ^\circ C \) recommended for the temperature of the immersion fluid was considered necessary, owing to the dependence on temperature of the dissolution rate of gelatin.

3.1.5.2 Dissolution test. The same considerations and procedures as those pertaining to tablets, given in section 2.1.5.2, are valid for capsules in respect of the dissolution test. A special problem encountered in testing the dissolution rate with paddle methods is that capsules tend to float. A practice commonly adopted to overcome this difficulty is to insert the capsule in a helix of inert wire before it is placed in the vessel.

3.2 Additional criteria for capsules resistant to gastric acids

For capsules not intended to disintegrate in a gastric medium the following modifications of the disintegration test, described in section 3.1.5.1, are recommended:

The procedure includes two steps, similar to those described in section 2.2.1.2. Hydrochloric acid (0.1 mol/l) is used for the acid integrity step of the procedure. It is then replaced by a phosphate buffer of pH 6.8 (in which it may sometimes be necessary to include pancreatin) for the disintegration step. The temperature of both liquids is maintained at \( 37 \pm 1 \, ^\circ C \). The capsules remain intact in the acid medium for 120 minutes, showing no signs of rupture or cracks, and disintegrate completely within 60 minutes in the phosphate buffer.

3.3 Quality criteria for slow release preparations in capsule form

The pertinent requirements are described in section 2.2.3.
Appendix 1

DISINTEGRATION APPARATUS

The apparatus consists of a basket-rack assembly, a suitable vessel for the immersion fluid (such as a 1-litre beaker), a thermostatic arrangement for maintaining the fluid at the required temperature, and a device for raising and lowering the basket-rack in the immersion fluid at a required constant frequency through the required distance. The volume of the fluid in the immersion vessel is such that at the highest point of the upward stroke the wire mesh which forms the bottom of the basket remains at least 2.5 cm below the surface of the fluid, while, at the lowest point of the downward stroke, it descends to not less than 2.5 cm from the bottom of the vessel. The time required for the upward stroke should be equal to the time required for the downward stroke, and the change in stroke direction should be a smooth transition rather than an abrupt reversal of motion.

The basket-rack assembly consists of 6 open-ended cylindrical glass tubes and a rack for holding them in a vertical position. The tubes are 75–80 mm long, have an inside diameter of about 21.5 mm and a wall about 2 mm thick. The tubes are held vertically by 2 superimposed plates, circular in shape and made of transparent plastic material, each about 9 cm in diameter and 6 mm thick, perforated by 6 holes of a diameter that allows the tubes to be inserted. The holes are equidistant from the centre of the plate and equally spaced one from another. A piece of woven gauze made of stainless steel wire about 0.635 mm in diameter with a mesh aperture of 2.0 mm is attached to the under side of the lower plate. The upper plastic plate is covered with a stainless steel disc, about 1 mm in thickness, of a diameter similar to that of the plastic discs. The steel disc is perforated by 6 holes about 22 mm in diameter positioned to coincide with those of the upper plastic plate and the upper open ends of the glass tubes. The disc fits over the tubes and holds them between the plastic plates. The plates are held rigidly 75–80 mm apart by vertical stainless steel rods at the periphery. A metal rod is fixed to the centre of the upper plate to enable the assembly to be attached to a mechanical device capable of suitably lowering and raising it.

The discs to be inserted into the tubes are cylindrical in shape, 20.6–20.8 mm in diameter and 9.4–9.6 mm thick. They are made of suitable transparent plastic material having a relative density of 1.18–1.20. Each disc is pierced by 5 holes 2 mm in diameter, 1 in the centre and the other 4 spaced equally on a circle with a radius of 6 mm from the centre of the disc. On the lateral surface of the disc, 4 equally spaced V-shaped grooves are cut in such a way that at the upper surface of the disc they are 9.5 mm wide and 2.55 mm deep, and at the lower surface 1.6 mm square.

Appendix 2

PLUNGER

(For use in the disintegration test of capsules)

The plunger is composed of two discs made of transparent plastic material, both mounted firmly (by force-fitting or gluing) on a central metal rod measuring 100 mm in length and about 2 mm in diameter. One of the discs, which is placed in about the middle of the rod, is 8.5 mm thick and has a rim on its upper surface. The diameter of
the lower surface of the disc is 20.5 mm, while that of the upper (including the rim) is 25 mm. The other disc, which is placed at the lower end of the rod, is 8 mm thick with a uniform diameter of 20.5 mm. Each disc is perforated vertically by 6 holes, 2.5 mm in diameter, which are equidistant from one another in a circle 11 mm in diameter. The gap between the discs is usually 45 mm. After the plunger is inserted, chambers 20–25 mm high remain at the lower end of the tubes of the disintegration apparatus. If the disintegration test is done on very large capsules which do not fit readily into the above-mentioned chambers, another set of plungers, with a smaller gap between the discs, should be used.

REFERENCES