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African Traditional Medicine — Quality and safety of raw materials and finished products made with raw materials — Part 1: General requirements

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This African Standard was prepared by ARSO *Technical Committee on African Traditional Medicine* (ARSO/TC 82)

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Introduction

This series consists of four parts with different content as shown in Figure 1

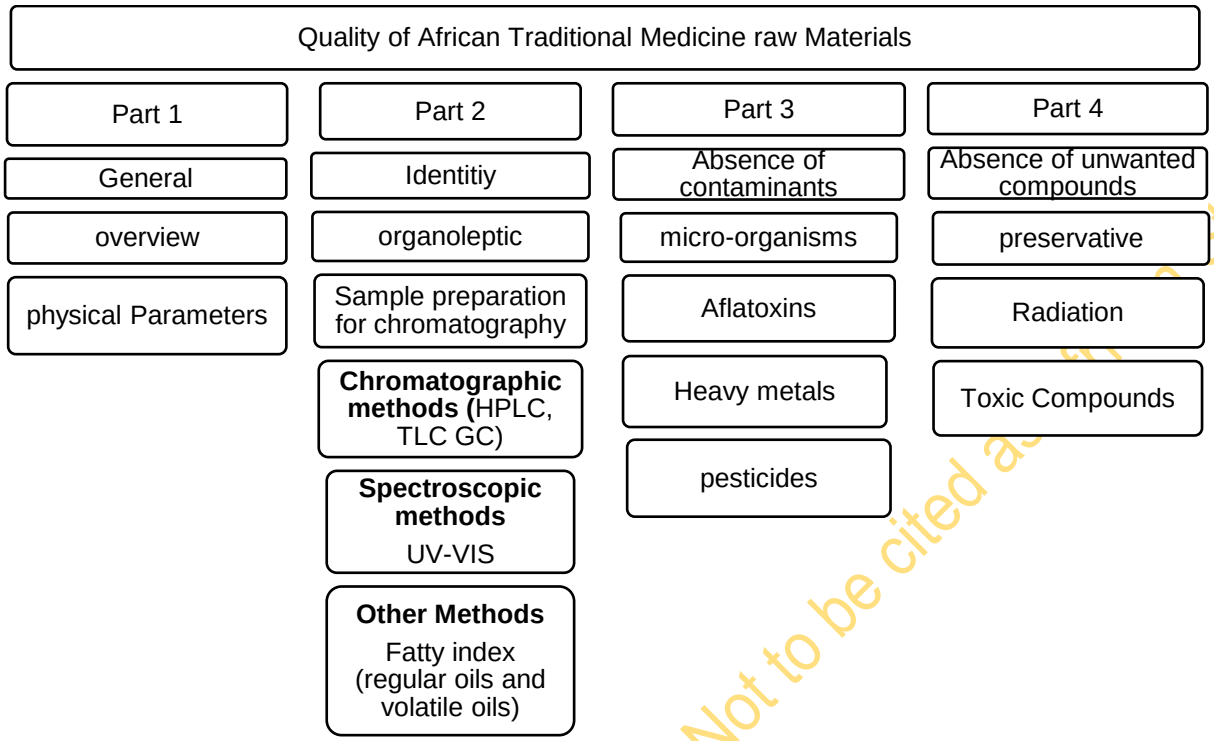


Figure 1 — Overview of Quality of African Traditional Medicine raw Materials

African Traditional medicine — Quality and safety of raw materials and finished products made with raw materials — Part 1: General requirements

1 Scope

This document specifies general requirements within a quality control framework for raw materials and finished products used in and as African Traditional Medicine (ATM) and derivative forms, and the comparison between the starting materials and the finished products, if necessary.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 19609 -1, *Traditional Chinese medicine — Quality and safety of raw materials and finished products made with raw materials — Part 1: General requirements*

ISO 760, *Determination of water — Karl Fischer method (General method)*

ISO 3310-1, *Test sieves — Technical requirements and testing — Part 1: Test sieves of metal wire cloth* ISO 10523, *Water quality — Determination of pH*

ISO 12937, *Petroleum products* — Determination of water — Coulometric Karl Fischer titration method

ISO 19609 -2, *Traditional Chinese medicine* — Quality and safety of raw materials and finished products made with raw materials — Part 2: Identity testing of constituents of herbal origin

ISO 22217, *Traditional Chinese medicine* — Storage requirements for Chinese materia medica and decoction pieces

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
finished product for modernized traditional therapy
concentrated product from hot aqueous decoctions of *decoction pieces* (3.2) or other starting materials (3.11) as well as powder made from starting materials described in pharmacopoeias, applied in the dosage forms of capsules, granules or tablets

3.2
decoction
prescription medicinal processed from traditional African medicinal material under the direction of ATM and processing methods for medicines and derivative forms, which can be directly used in clinical practice or the production of prepared medicines

3.3 disintegration
physical breakdown of a material into very small fragments in a pharmaceutical context except insoluble coating materials or broken capsule shell

3.5
dissolution
process of obtaining a solution containing the analyte of interest in a pharmaceutical context

3.6
finished product
commercial product intended for sale and use, including *decoction pieces* (3.3)

3.7
foreign matter
material consisting of any or all foreign tissues (matter coming from the source plant but not defined as the right herbal material) and foreign elements (other matter of vegetable, animal or mineral origin)

3.8
non-traditionally produced finished product for phytotherapy
product made from ATM raw materials (3.9) which are not *decoction pieces* (3.3) or *finished products for modernized traditional therapy* (3.2)

3.9
raw material
substance going into or involved in the manufacturing of a bulk product

3.10
residual solvent
organic volatile chemical used or produced in the manufacturing of extracts or excipients or in the preparation of medicinal products, and not completely removed by practical manufacturing techniques

3.11
starting material
material received by a manufacturer to be commercially processed, manufactured or packaged

Note 1 to entry: This includes raw materials (3.9) and other materials, for example solvents, excipients and capsule shells.

3.12
phytotherapy

the study of the use of extracts of natural origin as medicines or health-promoting agents
.

4 Overview of herbal medicinal products

4.1 Raw materials

Raw materials of ATM are:

a) herbal material (e.g. flowers, herbs, seeds, fruits, roots and other parts of medicinal plants, fresh juices, gums, natural essential oils, resins);
b) parts of animals and animal products, eg. Bones, hoofs, milk etc.
c) minerals.

4.2 Products of raw materials

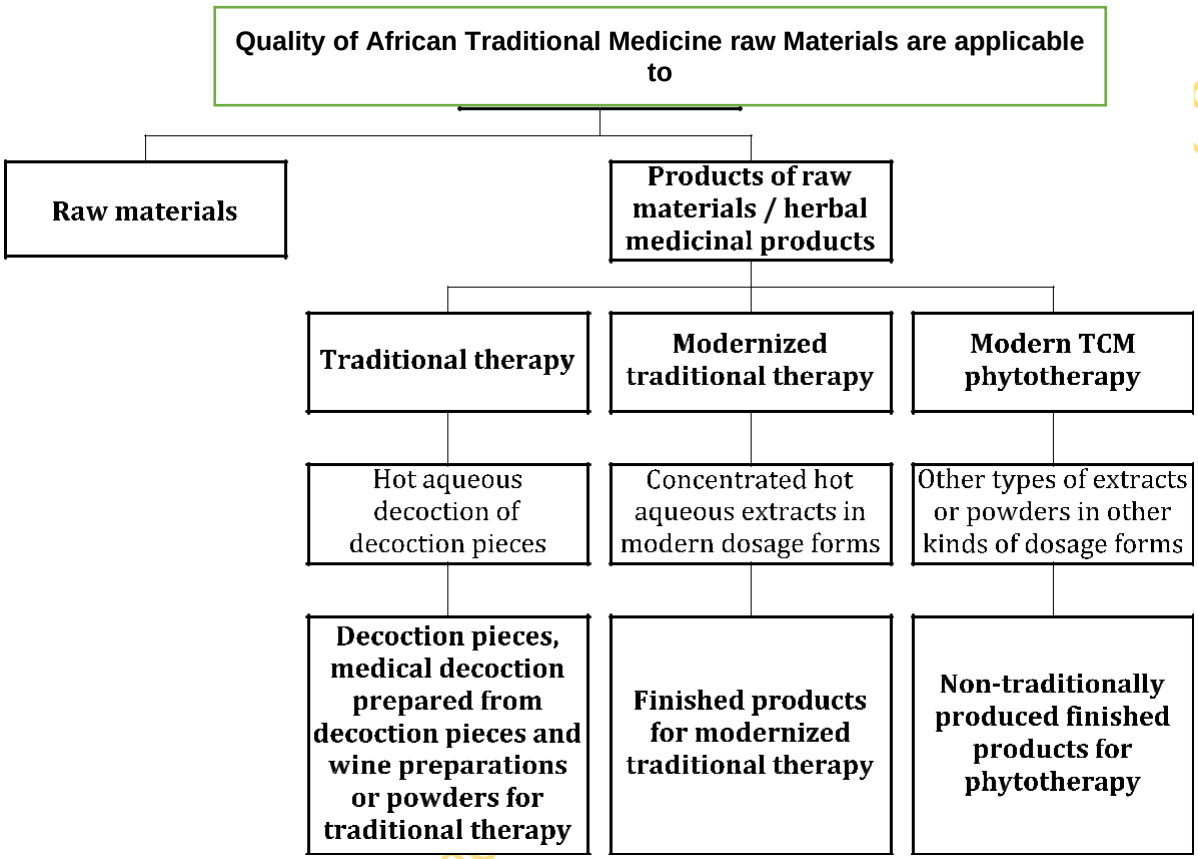
4.2.1 General

Products of raw materials are divided into three groups depending on the form of therapy:

a) decoction pieces, medicinal decoction prepared from decoction pieces and wine preparations or powders for traditional therapy;

b) finished products for modernized traditional therapy (e.g. capsules, coated and uncoated tablets, powders and granules);

c) non-traditionally produced finished products for phytotherapy (e.g. regulated formulas as remedies, made from extracts with other solvents instead of water).



4.2.2 Decoction pieces, medicinal decoctions prepared from decoction pieces and wine preparations or powders

The typical raw materials used in and as ATM are decoction pieces in the form of cut raw materials. These are intended to produce a preparation using hot or boiling water.

NOTE 1 In the classical ATM therapy, herbal and animal material as well as minerals were cut into smaller pieces and used during or after a processing step (e.g. steaming, cooking, calcinating) as a source for the individual mixture after a practitioner's or doctor's prescription.

NOTE 2 In some cases, wine can be used as a solvent instead of Water

4.2.3 Finished products for modernized traditional therapy

Finished products for modernized traditional therapy are:

a) concentrates from hot aqueous preparations;

NOTE 1 Only hot water decoctions can be seen as typically traditional, without toxicity risks.

NOTE 2 Traditionally produced wine preparation can also be used.

b) powders made from raw materials which are described in the Chinese[10], Japanese[11] and Korean[9] pharmacopoeias;

NOTE 3 In the case of powdered materials, there are risks for the patients because of the potential toxicity of the raw materials.

c) capsules, coated and uncoated tablets, powders and granules as dosage forms based on a) or b).

NOTE 4 The toxic risks cannot be extrapolated from traditional use of the decoctions. A lot of lipophilic compounds can be seen as toxic (e.g. aristolochic acid, which was not a problem in decoctions in ATM). The toxic risks of lipophilic compounds do not appear in water decoctions, but in powders, alcoholic extracts and lipophilic concentrates.

4.2.4 Non-traditionally produced finished products for phytotherapy

Non-traditionally produced finished products for phytotherapy are raw materials and products not listed in 4.2.2 and 4.2.3.

The pharmacology and toxicology of these products shall be tested by the producer before marketing.

NOTE 1 ATM products can be seen in parallel to the “European Phytomedicine”.

NOTE 2 KAMPO products extracted with up to 30 % ethanol do not need to be declared in Japan.

NOTE 3 For the markets in Europe and associated countries a registration is required for each product independent of specific dosage forms.

NOTE 4 Products made with supercritical carbon dioxide are not allowed in countries which apply the *European Pharmacopoeia*[14].

5 Quality testing

5.1 General

The quality of therapeutics is internationally defined with three general criteria: potency, safety and accuracy. These criteria are also relevant for ATM therapeutics (see Figure 3).

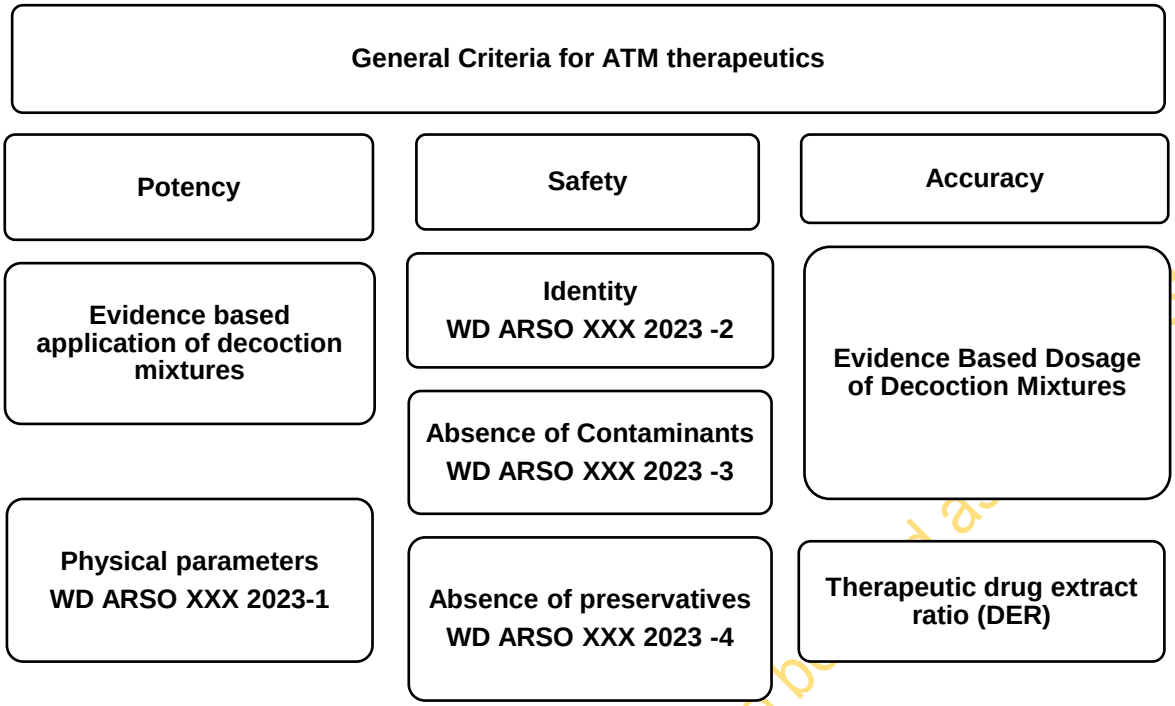


Figure 3 — General criteria for ATM therapeutics

Quality criteria of raw materials and products of raw materials are defined in the ISO 19609 series as follows:

— correct physical parameters;

— correct identity of herbal ingredients;

— absence of contaminants;

— absence of preservatives and unwanted compounds where applicable

5.2 Testing procedure

Products of raw materials shall be tested for physical parameters, if applicable, in accordance with Clause 6.

Products of raw materials shall be tested for the identity of the herbal ingredients in accordance with ISO 19609-2.

Products of raw materials shall be tested for the absence of contaminants.

Products of raw materials shall be tested for the absence of preservatives and unwanted compounds for individual materials.

The requirements and methods are typically unique for a specific dosage form and listed also in the different pharmacopoeias.

6.2 Sampling

6.2.1 General

In order to reduce the effect of inhomogeneity of the sample in qualitative and quantitative analysis, the composition of the sample used shall be representative of the batch of material being examined.

6.2.2 Bulk sampling method

The bulk sample shall be collected by combining and thoroughly mixing the part samples taken from containers, bales and bags.

One part sample from each container shall be sampled. Samples shall be taken from the upper, middle and lower section of the container and shall be combined so that the samples are representative of different parts of the containers.

In the case of large bales or bags, samples shall be taken from a depth of at least 10 cm.

6.2.3 Test sampling method

6.2.3.1 General

The reduction of the size of the bulk sample shall be done by the method of quartering or other appropriate methods.

Other appropriate methods that produce a homogeneous sample may be used, making sure that each retained portion remains representative of the whole.

The minimum retained quantity of the test samples shall conform to the conditions in Table 1.

Table 1 — Minimum weight of test samples

Type of herbal material	Minimum weight of test sample
Roots, rhizomes, bark, herbs	250 g or mass of whole sample if bulk sample is less than 250 g
Leaves, flowers, seeds, fruits	125 g or mass of whole sample if bulk sample is less than 125 g
Broken or fragmented crude materials (where the average mass of the pieces is less than 0,5 g)	75 g

After reduction of sample size a test for foreign matter shall be done.

For the preparation of the test samples for chemical and chromatographic analysis, as well as for determination of microscopic characteristics, a milling and sieving process is necessary.

ANNEX A
(normative)

A. Procedures for sample Preparation

A.1 Apparatus

Use the usual laboratory equipment and, in particular, the following.

A.2 **Analytical balance**, weighing to an accuracy of 1 mg.

A.3 **Milling apparatus**.

A.4 **Sieves**, with 1 mm and 0,355 mm screen in accordance with ISO 3310-1

A.5 Procedure for producing specific test samples

A.5.1 Quartering

The bulk sample shall be placed after thoroughly mixing as a level and square-shaped heap. The material shall be divided diagonally into four equal parts. Two opposite quarters shall be retained and carefully remixed. The process shall be repeated as necessary until the required minimum mass (see Table 1) is obtained for the test sample.

A.5.2 Test for foreign matter

Herbal materials should be free of mould, insects and other animal contaminants. Accepted levels of foreign matter are documented in the relevant monographs.

Materials identified visually as foreign matter shall be separated manually and weighed with an analytical balance.

The content of foreign matter shall be calculated as a percentage of the whole test sample. The result shall be documented.

A.5.3 Preparing test samples for chemical and chromatographic analysis

The test sample shall be milled and sieved through a 1 mm screen or the screen size specified in a specific monograph. The use of a milling machine is recommended.

The residue retained on the sieve shall not be more than 10 % of the total mass of the milled sample.

In those cases where this requirement cannot be met because of physical specifities of the raw material, the test sample for analysis shall be composed of the two parts measured separately. Therefore, the quantity required for each analysis shall be derived by weighing proportional quantities of the powder and the residue.

A.5.4 Preparing test samples for determination of microscopic characters

A portion of the milled test sample (see 6.2.3.3.3) shall be re-milled and sieved through a 0,355 mm screen or a finer screen.

NOTE The details of microscopic characterization are also described in ISO 19609-2 and ISO/TS 21310.

A.6 Estimation of the water content of herbals and resulting products

A.6.1 General

The water content should be not higher than 10 %, because this reduces the stability of dried raw materials and resulting products made from herbal materials. Different water contents are specified in the individual monographs.

NOTE On one hand chemical reactions need, in a high number of reaction types, water as solvent or as reagent. On the other hand, higher amounts of residual water in raw materials as well as in ready products are, together with organic substances and temperature, the best growing conditions for microorganisms and their degradation of substrate.

A.6.2 Testing methods

A.6.2.1 General

For the estimation of the water content one of the following methods shall be used:

— loss on drying (see A.6.2.2);
— quantitative analysis of water content (see A.6.2.3).

A.6.2.2 Loss on drying

A.6.2.2.1 General

The estimation of the loss on drying is a method to estimate the total content of water and other volatile constituents, for example essential oils. In accordance with the expected content of these volatile constituents, one the following methods shall be used:

— method for raw materials and products with no or low content of essential oils;

— method for raw materials and products with higher content of essential oils;

— method for raw materials and products with unstable constituents.

A.6.2.2.2 Sample preparation

In a flat-bottomed weighing bottle about 50 mm in diameter and 30 mm in height quickly weigh about 0,50 g of the material or product to be examined in powdered form.

A.6.2.2.3 Reagents

A.6.2.2.3.1 Diphosphorus pentoxide.

A.6.2.2.3.2 Anhydrous silica gel.

A.6.2.2.4 Apparatus

Use the usual laboratory equipment and, in particular, the following.

A.6.2.2.4.1 Analytical balance, weighing to an accuracy of 0,1 mg.

A.6.2.2.4.2 Desiccator.

A.6.2.2.4.3 Laboratory oven (100 °C to 105 °C), if applicable.

A.6.2.2.4.4 Vacuum unit (1,5 kPa to 2,5 kPa), if applicable.

A.6.2.2.5 Method for raw materials and products with no or low content of essential oils

Drying shall be done in an oven at 100 °C to 105 °C for 3 h. After cooling in a desiccator over diphosphorus pentoxide or anhydrous silica gel, the material shall be weighed. The calculation of the result shall be expressed as a mass percentage.

A.6.2.2.6 Method for raw materials and products with higher content of essential oils

Drying of the material shall be done to constant mass in a desiccator. The drying shall be carried out over diphosphorus pentoxide at atmospheric pressure and at room temperature. After weighing, the result shall be calculated and expressed as a mass percentage.

A.6.2.2.7 Method for raw materials and products with unstable constituents

Drying of the material shall be done to constant mass *in vacuo* in a desiccator. The drying is carried out over diphosphorus pentoxide at a pressure of 1,5 kPa to 2,5 kPa at room temperature. After weighing, the result shall be calculated as a mass percentage.

A.6.2.3 Quantitative analysis of water content

A.6.2.3.1 General

The estimation of the quantitative analysis of water content is a method to estimate the total content of water. One of the following methods shall be used:

— titration according to Karl Fischer in accordance with ISO 760;

— coulometric determination of water in accordance with ISO 12937;

— determination of water with distillation;

— determination of water with gas chromatography with thermal conductivity detector (TCD) (see A.6.2.3.2).

A.6.2.3.2 Determination of water with gas chromatography with thermal conductivity detector (TCD)

A.6.2.3.2.1 Sample preparation

50 mg of powdered test sample shall be correctly weighed. The resulting powder shall be dissolved in 200 µl of dried dimethyl sulfoxide (DMSO) in a disposable special dried vial.

A.6.2.3.2.2 Reagents

Dried DMSO.

A.6.2.3.2.3 Apparatus

Use the usual laboratory equipment and, in particular, the following:

Gas chromatograph, with TCD.

A.6.2.3.2.4 Procedure and analytical conditions

The gas chromatography with TCD shall be done following the conditions in Table 2.

Table 2 — Conditions for gas chromatography analysis

Solvent	DMSO		
Column	Gas chromatography (GC) column packed with 6 % cyanopropylphenyl/94 % di-methylpolysiloxan or another appropriate stationary phase material		
Gradient	Time	Temperature	Slope
	0 min	40 °C	
	2 min	40 °C	
	18 min	200 °C	10 °C/min
Detection	TCD		
Conditions	Carrier	Helium 45 kPa	
	Injector temperature	250 °C	
	Detector temperature	TCD 260 °C	
	Sensitivity	0 - 1 000 mV	
	Record interval	18 min	
	Injection volume	1 µl	

Table 2 *(continued)*

Test sample	50 mg correctly weighed compound dissolved in 200 µl of dried DMSO in a disposable special dried vial
Estimation limit	< 0,05 %

Other appropriate and valid testing methods can be used.

ANNEX B
(Normative)

B. Requirements and testing methods for finished products for modernized traditional therapy and non-traditionally produced finished products for phytotherapy

B.1. General

Finished products for modernized traditional therapy and non-traditionally produced finished products for phytotherapy shall fulfil the requirements for pharmaceutical products.

An active substance of a ATM product shall be only the raw material (appropriate herb powders or extracts from one or more herbs in a homogenious mixture) with a declared content of all excipients.

B.2. Estimation of the uniformity of dosage units

B.2.1 Estimation of the uniformity of mass

B.2.2. Apparatus

Use the usual laboratory equipment and, in particular, the following.

B.2.2.1 **Analytical balance**, weighing to an accuracy of 0,1 mg.

B.2.3. Procedure

B.2.2.1. Multidose preparations

Individually 20 units shall be taken at random and shall be weighed and the average mass shall be determined.

B.2.2.2. Single-dose preparations

Individually 20 individual containers shall be taken at random, the content shall be weighed and the average mass shall be determined.

B.2.2.3 Calculation

No more than two of the individual masses shall deviate from the average mass by more than the percentage deviation shown in Table 3 and none shall deviate by more than twice that percentage.

Table 3 — Percentage deviation of average mass of solid dosage forms

Pharmaceutical form	Average mass	Percentage deviation
Tablets (uncoated and film-coated)	80 mg or less	10 %
	More than 80 mg and less than 250 mg	7,5 %
	250 mg or more	5 %
Capsules, granules (uncoated, single-dose and powders (single-dose)	Less than 300 mg	10 %
	300 mg or more	7,5 %

Table 3 *(continued)*

Pharmaceutical form	Average mass	Percentage deviation
Powders for parenteral administration (single-dose)	More than 40 mg	10 %

B.2.3 Estimation of the uniformity of mass of delivered doses from multidose containers

B.2.3.1 General

The following test is intended for oral dosage forms such as granules, powders for oral use and liquids for oral use, which are supplied in multidose containers provided at manufacture with a measuring device.

B.2.3.2 Apparatus

Use the usual laboratory equipment and, in particular, the following.

B.2.3.2.1 **Analytical balance**, weighing to an accuracy of 0,1 mg.

B.2.3.2.2 Procedure

Individually, 20 doses taken at random from one or more containers with the measuring device provided shall be weighed and the individual and average masses shall be determined.

B.1.2.2.4 Calculation

No more than two of the individual masses shall deviate from the average mass by more than 10 % and none shall deviate by more than 20 %.

B.1.3 Disintegration test for solid dosage forms like tablets and capsules

B.1.3.1 General

This test is provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium under the conditions of the experiment.

NOTE This test method is harmonized with the European[14], Japanese[11] and US[15] pharmacopoeias.

For the purposes of this test, disintegration does not imply complete dissolution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the discs, if used, is a soft mass.

Use apparatus for tablets and capsules that are not greater than 18 mm long with a basket-rack A and a related disc. For larger tablets or capsules use the same apparatus with a basket-rack B and a related disc.

B.1.3.2 Apparatus

Use the usual laboratory equipment and, in particular, the following.

B.1.3.2.1 Disintegration apparatus

The apparatus consists of a basket-rack assembly, a 1 l low-form beaker, 149 mm ± 11 mm in height and having an inside diameter of 106 mm ± 9 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35 °C and 39 °C, and a device for raising and lowering the basket in the

immersion fluid at a constant frequency rate between 29 cycles and 32 cycles per minute, through a distance of 55 mm ± 2 mm.

The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged.

The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

An alternative apparatus can be used after an approval of suitability and after validation.

B.1.3.2.2 Basket-rack assembly A for tablets and capsules of normal size not greater than 18 mm

The basket-rack assembly consists of six open-ended transparent tubes, each 77,5 mm ± 2,5 mm long and having an inside diameter of 21,85 mm ± 1,15 mm and a wall 1,9 mm ± 0,9 mm thick. The tubes are held in a vertical position by two plates, each 90 mm ± 2 mm in diameter, with six holes, each 24 mm ± 2 mm in diameter, equidistant from the centre of the plate and equally spaced from one another. Attached to the underside of the lower plate is a stainless-steel mesh, which has a plain square weave with 2,0 mm ± 0,2 mm mesh apertures and a wire diameter of 0,615 mm ± 0,045 mm. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

B.1.3.2.3 Basket-rack assembly B for tablets and capsules greater than 18 mm

The main part of the apparatus is a rigid basket-rack assembly supporting three cylindrical transparent tubes 77,5 mm ± 2,5 mm long, 33,0 mm ± 0,5 mm in internal diameter and with a wall thickness of 2,5 mm ± 0,5 mm. Each tube is provided with a cylindrical disc. The tubes are held vertically by two separate and superimposed rigid plastic plates 97 mm in diameter and 9 mm thick, with three holes. The holes are equidistant from the centre of the plate and equally spaced. Attached to the underside of the lower plate is a piece of stainless-steel mesh 0,63 mm ± 0,03 mm in diameter and having mesh apertures of 2,0 mm ± 0,2 mm. A metal rod is also fixed to the centre of the upper plate to enable the assembly to be attached to a mechanical device capable of raising and lowering it smoothly at a constant frequency of between 29 cycles and 32 cycles per minute, through a distance of 55 mm ± 2 mm.

Other suitable racks can be used.

B.1.3.2.4 Discs for basket-rack assembly A for tablets and capsules of normal size not greater than 18 mm

Each tube is provided with a cylindrical disc 9,5 mm ± 0,15 mm thick and 20,7 mm ± 0,15 mm in diameter. The disc is made of a suitable, transparent plastic material having a specific gravity of 1,18 to 1,20 and five parallel 2 mm ± 0,1 mm holes extend between the ends of the cylinder. One of the holes is centred on the cylindrical axis. The other holes are centred 6 mm ± 0,2 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centres of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1,6 mm ± 0,1 mm and its bottom edges lie at a depth of 1,5 mm to 1,8 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9,4 mm ± 0,2 mm and its centre lies at a depth of 2,6 mm ± 0,1 mm from the cylinder's circumference. All surfaces of the disc are smooth.

Other suitable discs can be used.

B.1.3.2.5 Discs for basket-rack assembly B for tablets and capsules greater than 18 mm

Each tube is provided with a cylindrical disc 31,4 mm ± 0,13 mm in diameter and 15,3 mm ± 0,15 mm thick, made of transparent plastic with a relative density of 1,18 to 1,20. Each disc is pierced by seven holes, each 3,15 mm ± 0,1 mm in diameter; one in the centre and the other six spaced equally on a circle of radius 4,2 mm from the centre of the disc.

Other suitable discs can be used.

B.1.3.3 Procedure

For tablets and capsules of normal size not greater than 18 mm, six tablets or capsules shall be tested. Place one dosage unit in each of the six tubes of the basket-rack A and add the related disc.

For tablets and capsules of greater than 18 mm, six tablets or capsules shall be tested. Place one dosage unit in each of the three tubes of the basket-rack B and add a related disc.

The operation of the apparatus shall be done with the defined test parameters for disintegration described in Table 4.

Table 4 — Test parameters for disintegration

Parameter	Value
Temperature	37 °C ± 2 °C or specified otherwise
Immersion fluid	1N HCl or specified otherwise
Disintegration time	30 min or specified otherwise

At the end of the specified time, lift the basket from the fluid and observe the dosage units.

B.1.3.4 Calculation

All of the dosage units shall be disintegrated completely.

If one or two dosage units for tablets and capsules of normal size not greater than 18 mm fail to disintegrate, repeat the test on 12 additional dosage units. The requirements of the test are met if not less than 16 of the 18 dosage units tested have disintegrated.

B.1.4 Estimation of particle size for powders and other small dosage forms

B.1.4.1 General

For powders and other small dosage forms, such as granules or compactates, the estimation of particle size shall be done by analytical sieving.

B.1.4.2 Apparatus

Use the usual laboratory equipment and, in particular, the following.

B.1.4.2.1 Test sieves in accordance with ISO 3310-1 and depending on the declaration of the particle size of the product.

Sieving tests can also be done with sieving machines according to ISO 9284.

B.1.4.3 Procedure

Assemble the appropriate sieves and operate in a suitable manner until sieving is practically complete. Weigh the separated fractions of the powders or granules.

B.1.4.4 Calculation

If a particle size is given, not less than 97 % of the powders or granules shall pass through the sieve.

Other appropriate testing methods can be used if they are validated.

B.1.5 Estimation of the pH-value of liquids, solutions or suspensions by potentiometric determination

B.1.5.1 General

The pH-value is the number which represents conventionally the concentration of hydrogen ions of an aqueous solution. The pH-value of a solution is related to that of a reference solution and calculated from the Nernst equation.

B.1.5.2 Procedure

The estimation of the pH-value of liquids, solutions or suspensions by potentiometric determination shall be done in accordance with ISO 10523 with appropriate equipment.

B.1.6 Dissolution test for solid dosage forms

B.1.6.1 General

This test shows the ability of the use of a solid dosage form, so that the active principles in the dosage form are available for the intended use. This test shall be used to determine the rate of release of active substances from solid dosage forms such as tablets and capsules.

The dissolution rate gives a calculative basis for the speed of release of specified active substances.

B.1.6.2 Reagents

B.1.6.2.1 Dissolution medium

A suitable dissolution medium is used. The volume specified refers to measurements made between 20 °C and 25 °C. If the dissolution medium is a buffered solution, adjust the solution so that its pH is within 0,05 units of the specified pH.

In general, an aqueous medium is used. The composition of the medium is chosen on the basis of the physico-chemical characteristics of the active substance(s) and excipient(s) within the range of conditions to which the dosage form is likely to be exposed after its administration. This applies in particular to the pH and the ionic strength of the dissolution medium.

The pH of the dissolution medium is usually set between pH 1 and pH 8. In justified cases, a higher pH may be needed. For the lower pH values in the acidic range, 0,1 M hydrochloric acid is normally used.

B.1.6.3 Apparatus

Use the usual laboratory equipment and, in particular, the following.

B.1.6.3.1 **Dissolution apparatus** with stirring paddles.

The dissolution apparatus consists of:

— a vessel, which may be covered, made of glass or other inert, transparent material;

— a motor;

— a drive shaft

— a stirring element.

The vessel is partially immersed in a suitable water-bath of any convenient size or heated by a suitable device such as a heating jacket. The water-bath or heating device permits the temperature inside the vessel to be maintained at 37 °C ± 0,5 °C during the test and the dissolution medium to be kept in constant, smooth motion.

An apparatus that permits observation of the preparation and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and a capacity of 1 l. Its height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.

The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results.

A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at a specified rate, within ± 4 %.

A paddle formed from a blade and a shaft is used as the stirring element. The vertical centre line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The distance of 25 mm ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert.

B.1.6.3.2 Apparatus for the quantification of active substances

Appropriate apparatus and methods for the estimation of the individual content of active substances shall be used.

Typical quantification methods include:

— quantitative high-pressure liquid chromatography (HPLC) analysis;

— quantitative thin layer chromatography (TLC) analysis;

— quantitative gas chromatography (GC) analysis;

— quantitative visible and ultraviolet (UV-VIS) spectrometry.

B.1.B.1 Procedure for the production of test sample solutions

Place the stated volume of the dissolution medium (±1 %) in the vessel and equilibrate the dissolution medium to 37 °C ± 0,5 °C.

Place one dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of non-reactive material, such as a few turns of wire helix, may be attached to dosage units that would otherwise float.

Operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating blade, not less than 1 cm from the vessel wall. Keep the vessel covered for the duration of the test and verify the temperature of the medium at suitable times.

Perform the analysis using a suitable assay method. Repeat the test with additional five dosage units or with a combination apparatus for six parallel tests.

Using the paddle apparatus, the volume of dissolution medium is normally 500 ml to 1 000 ml. A stirring speed of between 50 r/min and 100 r/min is normally chosen; it shall not exceed 150 r/min.

B.1.6.5 Estimation of the content of active substances in the test sample solutions

The test sample solutions shall be filtered through an appropriate filter and afterwards analysed with the individual estimation methods (see B.1.6.3.2).

B.1.6.6 Calculation

The quantity of active substance dissolve in the prescribed time shall be expressed as a percentage of the content stated in the declaration.

Other appropriate testing methods can be used if they are validated.

ANNEX C
(Informative)

C.1 Estimation of the content of residual solvents

C.1.2 General

Non-traditionally produced finished products for phytotherapy are characterized typically by the use of non-aqueous extracts. In this case organic solvents and in some cases supercritical carbon dioxide are used for extraction. According to internationally accepted theories, residual solvents must be quantified. Limits are applied nationally.

NOTE The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) document *Impurities: Guideline for Residual Solvents Q3C(R6)*[16] prescribes limits for the content of solvents which can remain in active substances, excipients and medicinal products after processing.

All substances and products shall be tested for the content of solvents likely to be present in a substance or product.

According to the ICH, typically used solvents can be categorized into three types:

— class 1, solvents to be avoided (see A.8.2.1);

— class 2, solvents to be limited (see A.8.2.2);

— class 3, solvents with low toxic potential (see A.8.2.3).

Testing shall be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of extracts, excipients or medicinal products. Medicinal products shall also be tested if a solvent is used during its manufacture.

When residual solvents are used, the methodology described in A.8.5 shall be applied wherever possible.
Otherwise, an appropriate validated method shall be employed.

When a quantitative determination of a residual solvent is carried out, the result is taken into account for the calculation of the content of the substance, except when a test for drying is carried out.

The test procedures described in A.8.6 shall be used:

— for the identification of the majority of residual solvents in a ATM product when the residual solvents are unknown;

— as a limit test for solvents when present in a ATM product.

C.1.3 Types of typically used solvents

C.1.3.1 Solvents to be avoided (class 1)

Solvents in class 1 (see Table 5) shall not be employed in the manufacture of extracts, excipients or medicinal products because of their unacceptable toxicity or their harmful environmental effect.

However, if their use is unavoidable in order to produce a medicinal product with a significant therapeutic advance then their levels shall be restricted.

Table 5 — Class 1, solvents that should be avoided

Solvent	Concern
Benzene	Carcinogen

Carbon tetrachloride	Toxic and environmental hazard
1,2-Dichloroethane	Toxic
1,1-Dichloroethene	Toxic
1,1,1-Trichloroethane	Environmental hazard

C.1.3.2 Solvents to be limited (class 2)

Solvents in class 2 (see Table 6) shall be limited in pharmaceutical products because of their inherent toxicity.

Table 6 — Class 2, solvents to be limited

Solvent	Solvent
Acetonitrile	Methanol
Chlorobenzene	2-Methoxyethanol
Chloroform	Methylbutylketone
Cyclohexane	Methylcyclohexane
1,2-Dichloroethene	N-Methylpyrrolidone
Dichloromethane	Nitromethane
1,2-Dimethoxyethane	Pyridine
N,N-Dimethylacetamide	Sulfolane
N,N-Dimethylformamide	Tetrahydrofuran
1,4-Dioxane	Tetralin
2-Ethoxyethanol	Toluene
Ethyleneglycol	1,1,2-Trichloroethene
Formamide	Xylene
Hexane	

C.1.3.3 Solvents with low toxic potential (class 3)

Solvents in class 3 (see Table 7) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

Table 7 — Class 3, solvents with low toxic potential

Solvent	Solvent
Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone

Table 7 *(continued)*

Solvent	Solvent
tert-Butylmethyl ether	Methylisobutylketone
Cumene	2-Methyl-l-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

C.2 Reagents

C.2.1 Dimethylformamide (DMF).

C.2.2 Sample preparation

For the analysis with GC a specific sample preparation shall be realized. In this case four different solutions shall be prepared (see Table 8).

Table 8 — Preparation of the different analytical solutions for GC analysis

No.	Solution	Preparation
1	Sample solution	Dissolve 0,200 g of the substance to be examined in DMF and dilute to 20,0 ml with the same solvent
2	Solvent solution	Dissolve appropriate quantities of the known (declared) solvents in DMSO and dilute to 100,0 ml with water
3	Blank solution	Prepare as described for solvent solution, but without the addition of solvent(s) (used to verify the absence of interfering peaks)
4	Test solution	Introduce 5,0 ml of the sample solution and 1,0 ml of the blank solution into an injection vial

Close the vials with a tight rubber membrane stopper coated with polytetrafluoroethylene and secure with an aluminium crimped cap. Shake to obtain a homogeneous solution.

In some cases this sample preparation procedure is not appropriate. In such cases the diluent to be used for the preparation of the sample solution and the static head-space conditions to be employed shall be demonstrated to be suitable and validated.

C.3 Apparatus

Use the usual laboratory equipment and, in particular, the following.

C.3.1 Gas chromatography apparatus with static head-space injection.

C.3.2 Procedure

The operating parameters (see Table 9) shall be applied for the GC analysis with static head-space injection

Table 9 — Operating parameters for the GC analysis with static head-space injection

No.	Operating parameters	Value
1	Equilibration temperature	105 °C
2	Equilibration time	45 min
3	Transfer-line temperature	110 °C
4	Pressurization time	30 s
5	Injection volume	1 µl
6	Temperature of the injection port	140 °C
7	Temperature of the detector	250 °C

The chromatographic conditions (see Table 10) shall be used in accordance with system A.

Table 10 — GC chromatographic conditions of system A

No.	Parameter	System A
1	Column	A fused-silica capillary or wide-bore column 30 m long and 0,32 mm or 0,53 mm in internal diameter coated with cross-linked 6 % polycyanopropylphenyl-siloxane and 94 % polydimethylsiloxane (film thickness: 1,8 µm or 3 µm)
2	Carrier gas	Nitrogen or helium for chromatography as the carrier gas
3	Pressure	Appropriate pressure of carrier gas
4	Split	Split ratio 1:5 with a linear velocity of about 35 cm/s
5	Detector	A flame-ionization detector (a mass spectrometer or an electron-capture detector may also be used)

The time program (see Table 11) for system A shall be applied.

Table 11 — Time program for system A

No.	Time	Temperature	Raise
1	0 min to 20 min	40 °C	
2	20 min to 40 min	≤ 240 °C	Raising 10 °C/min
3	40 min to 60 min	240 °C	

If there is an interference from the matrix analysed with system A, an additional analysis with system B shall be made.

The chromatographic conditions (see Table 12) shall be used in accordance with system B.

Table 12 — GC chromatographic conditions of system B

No.	Parameter	System B
1	Column	A fused-silica capillary or wide-bore column 30 m long and 0,32 mm or 0,53 mm in internal diameter coated with macrogol 20 000 (film thickness: 0,25 µm)
2	Carrier gas	Nitrogen or helium for chromatography as the carrier gas
3	Pressure	Appropriate pressure of carrier gas
4	Split	Split ratio 1:5 with a linear velocity of about 35 cm/s
5	Detector	A flame-ionization detector (a mass spectrometer may also be used or an electron-capture detector)

The time program (see Table 13) for system B shall be applied

Table 13 — Time program for system B

No.	Time	Temperature	Raise
1	0 min to 20 min	50 °C	
2	20 min to 39,2 min	≤ 165 °C	Raising 6 °C/min
3	39,2 min to 60 min	165 °C	

C.3.3 System suitability

Inject 1 µl of the gaseous phase of reference solution onto the column described in system A and record the chromatogram under such conditions that the resolution between acetonitrile and methylene chloride can be determined. The system is suitable if resolution between acetonitrile and methylene chloride is at least 1,0.

Inject 1 µl of the gaseous phase of the test solution onto the column described in system A.

C.3.4 Calculation

The mean area of the peak of the residual solvent(s) in the chromatograms obtained with the test solution is not greater than the mean area of the peak of the corresponding residual solvent(s) in the chromatograms obtained with a specific reference solution.

The test is not valid unless the relative standard deviation of the differences in areas between the analyte peaks obtained from three replicate paired injections of reference solution and the test solution is no more than 15 %.

If, in the chromatogram obtained, there is no peak which corresponds to one of the residual solvent peaks in the chromatograms obtained with solvent solution, then the substance to be examined contains no residual solvents.

If there is a solvent peak, a quantitative estimation shall be done.

The quantification of solvent contents shall be done in an appropriate way. Other approriate and valid methods can be used.

ANNEX D
(Informative)

D.1 Stability of ATM products

D.1.1 General

Stability testing of pharmaceutical products is an integral part of quality and safety. A great number of different testing methods are established worldwide.

D.1.2 Estimation of the stability of ATM products

For the estimation of the stability of ATM products two relevant conditions shall be considered:

— storage stability of individual herbal materials and products (internal degradation);

— storage conditions of individual herbal materials and products (storage requirements).

The storage stability of herbal materials and products shall be demonstrated by an appropriate analytical method.

For the confirmation of the storage stability of herbal materials and products, the typical quality-testing methods of the specific monographs or, if not established as an HPLC analysis, the proposed general identity and quality-testing method from ISO 19609-2 can be used for the qualification.

The storage conditions of individual herbal materials and products shall be considered in accordance with ISO 22217

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