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Traditional Chinese medicine — Quality and safety of raw materials and manufacturing products made with raw materials —

Part 2: Identity testing of constituents of herbal origin

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 249, *Traditional Chinese medicine*.

A list of all parts in the ISO 19609 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The ISO 19609 series consists of four parts with different content as shown in Figure 1.

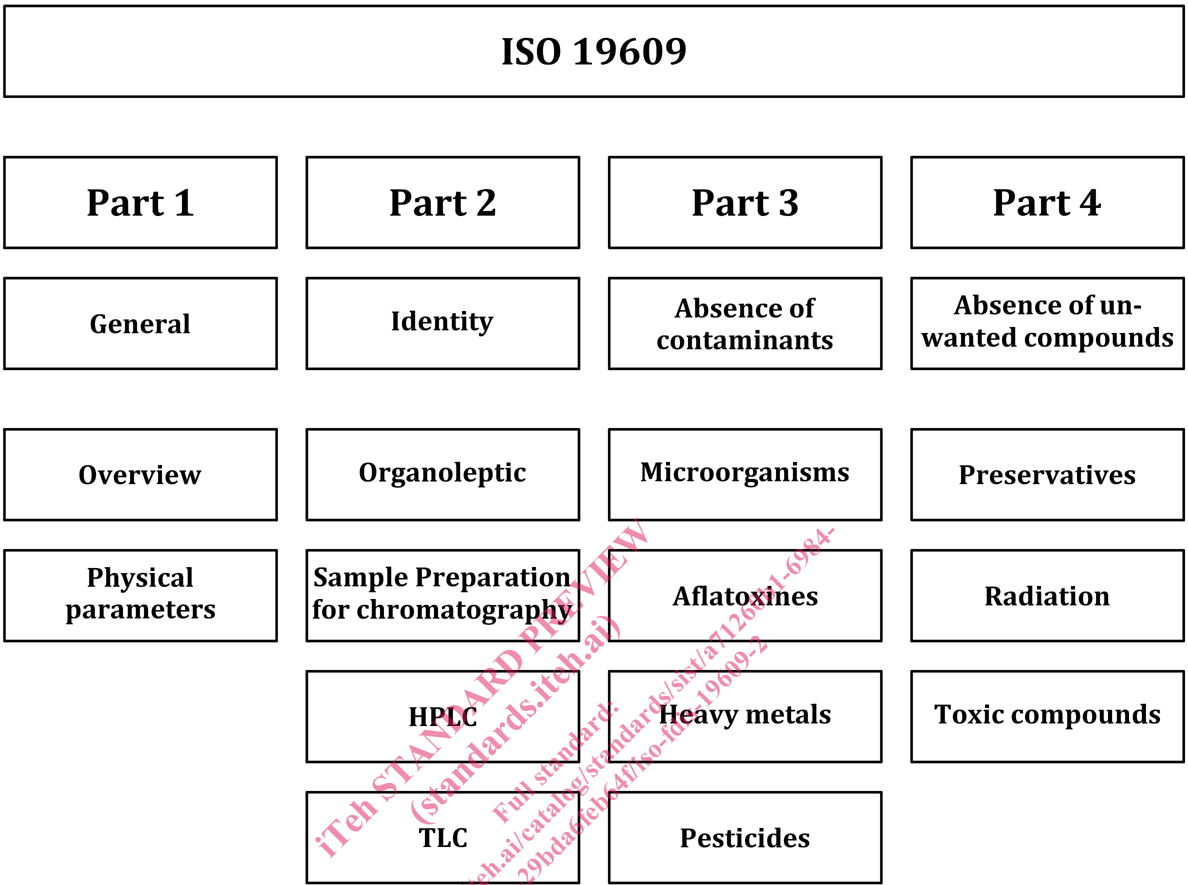

Figure 1 — Overview of the ISO 19609 series

To ensure the safety and efficacy of herbal medicinal products, it is imperative to check the identity of the raw materials and the finished products. One of the aims of the identity check is to prevent the accidental use of falsifications. In order to ensure safety, it is also essential to establish adequate simple testing methods.

As a general basis we can expect in a typical medicinal plant about 1 million constituents. When specific extracts are made from this plant, the number of ingredients is reduced to about 50 000. In classical phytochemical analysis, only one compound is usually analytically identified or quantified as a so-called marker without consideration of the secondary substance matrix from this multicomponent mixture. This results from the test practice for synthetic chemical monopreparations, in which the efficacy is based only on a high-dose active substance. This practice results from the analytical quantification of the relevant effective plasma concentration in the blood of the treated patients.

Phytopharmaceuticals are not based on only one active substance, but on a combination of synergistic compounds (many to thousands). Classical phytotherapy worldwide does not usually use only individual herbs but combinations of several herbs in preparations containing a correspondingly higher number of individual compounds (multitarget theory).

The analytical methods of the pharmacopoeias use one or more marker compounds without significance for the respective effectiveness. This cannot reflect the difficulty of synergistic substances as mentioned previously.

For preparations based on several raw herbal materials or extracts there are currently no test methods available. In the Chinese Pharmacopoeia[5], only one or two markers are often used for such finished products, although many more different raw materials are integrated.

Legally, the quality of these products as remedies must be estimated in an appropriate way.

For analytical quality assessment of such combinations, there are thus two basic approaches:

1) Marker-based identification test

   For each herbal raw material or extract used, a test methodology that can be implemented in the entire product must be individually redeveloped and validated for each of the associated markers. For a combination product with six herbals, herbal parts or exudates, as well as animals and minerals, six independent test methods for each single material based on these six marker compounds are required for release. This approach is currently mandatory for phytopharmaceuticals in countries which apply the European Pharmacopoeia[9].

2) Three-dimensional ingredient overview chromatography (fingerprint)

   With this novel valid method, it is possible to record the entire visible and ultraviolet (UV-VIS) spectroscopic detectable ingredient spectrum of a combination product (finished product) with only one liquid chromatographic separation method [one high-pressure liquid chromatography (HPLC) run instead of *x* different ones]. In comparison with corresponding reference extracts of the associated individual materials, this is a clear assignment without compulsory use of the various expensive marker substances possible. This makes a cost-effective, reliable and fast product release possible, without sacrificing product quality.

NOTE Experts agree that the presence of a marker compound as the only criterion for the identity of the used material is not sufficient. Experience of recent years has shown that synthetic active principles or only defined marker constituents were used instead of the real herb material (ephedra problem). Over a long time, high risks resulted from the addition of a racemic mixture of ephedrine to optimize the ephedra material (with a mixture of natural and non-natural isomers), which led in the end to a total prohibition of this material worldwide.

As a method for determining adequate identity, a non-specific HPLC fingerprint method is suitable. This method makes it possible to ensure the identity of the material, both in terms of the retention times of various ingredient patterns and in terms of the UV-VIS-spectra of the individual signals.

Here the question arises as to whether an individualized testing method for each herb (as mostly required in pharmacopoeias) or a general fingerprint method over the whole range of ingredients is to be used. The disadvantage of a method which is not optimally matched to each single herb, however, is easily outweighed by the advantage that complex mixtures of different raw materials in the resulting product can also be identified only with one single method. In addition, the found distribution pattern can give further conclusions on the used extraction procedure.

A universal method must be established over the entire hydrophilic to lipophilic region to realize efficiently the plurality of components in one analytical method, in a sufficiently secure way, with a photodiode array detection (PDA) as well as a diode array detection (DAD). Now the achieved spectra can become assigned to the underlying components of the individual raw materials. In exceptional cases it might be necessary to make certain improvements for individual products which have to be analysed (modification of one of the three-dimensional specifications: time, intensity and spectrum).

Traditional Chinese medicine — Quality and safety of raw materials and manufacturing products made with raw materials —

Part 2:
Identity testing of constituents of herbal origin

1 Scope

This document specifies requirements for identity testing within a quality control framework for raw materials and finished products used in and as traditional Chinese medicine (TCM) and derivative forms. It is applicable to natural products used in TCM, including starting materials and finished products of herbal origin.

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 manufacturing products made with raw materials — Part 1: General requirements*

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
active substance
substance of physiological or pharmacological action

3.2
decoction piece
prescription medicinal processed from Chinese Materia Medica under the direction of TCM and processing methods for Chinese medicines and derivative forms, which can be directly used in clinical practice or the production of prepared medicines

[SOURCE: ISO 18668-1:2016, 3.3, modified — Note 1 to entry amalgamated with definition.]

3.3
finished product
commercial product intended for sale and use, including *decoction pieces* (3.2)

3.4
manufacturing
process that creates a *finished product* (3.2) from a *starting material* (3.8) in a form suitable for its intended purpose, including packaging

3.5
monograph
detailed written study of a single specialized subject or an aspect of it

EXAMPLE Description of a herb in a pharmacopoeia.

3.6
raw material
substance going into or involved in the *manufacturing* (3.4) of a bulk product

[SOURCE: ISO 22716:2007, 2.28]

3.7
Rf-value
distance travelled by a given component divided by the distance travelled by the solvent front in thin layer chromatography

3.8
starting material
material received by a manufacturer to be commercially processed, manufactured or packaged

Note 1 to entry: This includes *raw materials* (3.6) and other materials, for example solvents, excipients and capsule shells.

4 Minimum requirements for the testing of the identity of starting materials and finished products

General quality control methods shall include the following identification tests and, if applicable, an "assay" as established in typical monographs:

a) macroscopic description test;

b) microscopic description test;

c) organoleptic description test;

d) test with high-performance liquid chromatography (HPLC);

e) test with thin layer chromatography (TLC).

The use of the methods depends on the material being tested (see Table 1).

Table 1 — Overview of identity testing methods for different materials

	Starting material with monograph	Starting material without monograph	Mixture of starting materials	Finished product
a) **macroscopic description test**	According monograph	According scientific literature	Not applicable	Not applicable
b) **microscopic description test**	According monograph	According scientific literature	According scientific literature	Not applicable
c) **organoleptic description test**	According monograph	According scientific literature	Not applicable	Not applicable
d) **HPLC test**	According monograph or alternative Clause 6	Clause 6	Clause 6	Clause 6
e) **TLC test**	According monograph or alternative Clause 6	Clause 6	Clause 6	Clause 6

5 Requirements for macroscopic, microscopic and organoleptic description tests

5.1 General

For sample collection see ISO 19609-1.

Visual and organoleptic examinations include the following three methods:

a) Macroscopic description test for identification of herbal materials.

This description consists of the form, size, colour, surface characters and texture (including cut surface or fracture characters) of the crude materials and prepared slices.

— "Form" refers to the shape of crude materials and prepared slices. Wrinkled herbs, leaves or flowers can be moistened, softened and spread.

— "Size" refers to the length, diameter and thickness of crude materials and prepared slices. In general, a milimetre ruler is used for the measurement.

— "Colour" refers to the colour and glossiness of crude materials and prepared slices observed in daylight. If the colour is described in a combination of two colours, the main colour is the latter.

— "Surface characters", texture and cut surface of crude materials or prepared slices is described without pretreatment.

b) Microscopic description test for identification of herbal materials.

Microscopic identification is a method where the application of a microscope is used to identify the characters of tissues, stomata and stomata index, cells or cell contents in sections, powders, disintegrated tissues or surface slides of prepared slices of crude materials and dosage form, including powders of prepared slices of crude materials. Representative samples are chosen to be identified and slides are prepared to meet the requirements of identification for each crude material.

If the samples being examined are pulverised or ground (e.g. in the case of decoction pieces), the resulting material should conform with the requirements in the monograph and ISO/TS 21310, as well as the general criteria.

c) Organoleptic description test for identification of herbal materials.

— Odour

— Taste

NOTE Historically, the exact visual examination of the herbs was the only criterion for identification. This is still used in addition to the described modern testing methods for starting materials. For uncut, cut and powdered herbal materials, microscopic, macroscopic and organoleptic tests are established.

5.2 Macroscopic description test

5.2.1 Application

Macroscopic description tests are applicable for starting materials. Mixtures of starting materials and finished products cannot be described typically by macroscopic description tests.

5.2.2 Macroscopic examination

The macroscopic examination is normally done without any apparatus for the description. The use of a magnifying glass or binoculars is appropriate for the macroscopic examination of test samples. The magnification shall be sufficient to allow adequate characterization of the smallest characters to be classified in the test sample. The use of an appropriate lamp is recommended.

5.2.3 Assessment

The examinations shall be compared with authenticated reference data from monographs or other reliable scientific data. If the results are identical with the reference data this part of the identity can be confirmed.

5.3 Microscopic description test

5.3.1 Application

Microscopic description tests are applicable for starting materials. Mixtures of starting materials and finished products cannot be described typically by microscopic description tests.

5.3.2 Microscopic examination

The sample collection shall be done in accordance with ISO 19609-1:2020, 6.2.

If the samples being examined are pulverised or ground (e.g. in the case of decoction pieces) the resulting material should conform with the requirements in the monograph.

The microscopic examination should be done in accordance with ISO/TS 21310 and can be applied to other materials, such as powdered herbals.

5.3.3 Assessment

The examinations shall be compared with authenticated reference data from monographs or other reliable scientific data. If the results are identical with the reference data this part of the identity can be confirmed.

