INTERNATIONAL STANDARD

ISO 23419

First edition
2021-12

Traditional Chinese medicine — General requirements for manufacturing procedures and quality assurance of granules

Médecine traditionnelle chinoise — Exigences générales relatives aux modes opératoires de fabrication et à l'assurance de la qualité des granules

Reference number
ISO 23419:2021(E)

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Published in Switzerland

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Foreword

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

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

Herbal medicines used in traditional Chinese medicine have been used as decoctions for thousands of years. However, from the aspect of advantage and convenience in preparation, portability and sanitation, dry extract preparations such as granules or compactates, tablets and capsules have been developed as alternative forms of dosage for decoctions. Decoction is still the most common form of dosage in China, Korea, Australia and many other countries. However, exceptionally in Japan, nearly 100 % of the Kampo product market is taken up by dry extract preparations. Application of dry extract preparations in other countries has increased in recent years and this is expected to continue.

Among the dry extract preparations mentioned above, granules and compactates are the most cost-effective forms of dosage made by simple manufacturing procedures. Although granules are listed in many pharmacopoeias as a major form of dosage, there is no standard specializing in granules made from medicinal plants. In the manufacturing procedure of granules of medicinal plants, there are many critical points to be taken into account. To obtain granules and compactates with consistent good quality and without major processing troubles during manufacturing, these critical points must be clarified and optimized prior to commercial production.

Traditional Chinese medicine — General requirements for manufacturing procedures and quality assurance of granules

1 Scope

This document specifies general requirements for manufacturing procedures and quality and safety assurance of granules and compactates made from traditional Chinese medicine extracts or powder for oral use. This document excludes granules or compactates made from pure compounds (chemically defined) even if they are isolated as naturally occurring constituents of decoction pieces or crude herbal and mineral drugs.

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 18664, *Traditional Chinese Medicine — Determination of heavy metals in herbal medicines used in Traditional Chinese Medicine*

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

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 19617, *Traditional Chinese medicine — General requirements for the manufacturing process of natural products*

ISO 21371, *Traditional Chinese medicine — Labelling requirements of products intended for oral or topical use*

ISO 22283, *Traditional Chinese medicine — Determination of aflatoxins in natural products by LC-FLD*

ISO 22467, *Traditional Chinese medicine — Determination of microorganism in natural products*

ISO 23723, *Traditional Chinese medicine — General requirements for herbal raw material and materia medica*

3 Terms and definitions

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

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

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

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

3.1
crude drug
medicinal part obtained from plants or animals, cell inclusions and secretions separated from the origins, their extracts and minerals

[SOURCE: ISO 19617:2018, 3.8, modified — Notes to entry removed.]

3.2
critical parameter
parameter whose variability has an impact on quality and productivity of each product or process

Note 1 to entry: Critical parameters depend largely on type and size of production devices as well as physical properties of matrices. Critical parameters can be individually verified and optimized prior to commercial production.

3.3
granules
coated or uncoated small grains which range from approximately 0,2 mm to 4 mm in diameter, made from a uniform mixture of powdered extract and excipients

Note 1 to entry: Granules are made from extracts or powder made from single or multiple herbs or decoction pieces. They are used instead of decoction pieces or instead of traditionally prescribed herbal recipes described in the classic medicine books of ancient China, such as Shanghan lun (傷寒論) and Jinguiyaolue (金匱要略), or books related to Kampo and Korean medicines.

Note 2 to entry: Granules are made from non-treated crude extracts or powder, or simple fractionated crude extracts, as far as they can be legally categorized as traditional Chinese medicine.

Note 3 to entry: Excipients are diluents or binders to improve lubricity and binding of extract powder for granulation.

3.4
compactate
irregular shaped agglomerate obtained directly from the dried extract by compaction

Note 1 to entry: Compactates are made from non-treated crude extracts or powder made from single or multiple herbs or decoction pieces. They are used instead of decoction pieces or instead of traditionally prescribed herbal recipes described in the classic medicine books of ancient China, such as Shanghan lun (傷寒論) and Jinguiyaolue (金匱要略), or books related to Kampo and Korean Medicines, as they can be legally categorized as traditional Chinese medicine.

3.5
dry extract
dried solid or *powder* (3.6) obtained from water or aqueous ethanol extracts of medicinal herbs or decoction pieces

Note 1 to entry: Sources of dry extract include minerals and herbal drugs.

3.6
powder
fine particles made through crushing or milling of medicinal herbs or decoction pieces

Note 1 to entry: Sources of powder include minerals and herbal drugs without solvent extraction.

3.7
out-of-specification lot
lot which failed quality criteria

3.8
granulation
process of particle enlargement by agglomeration technique with and without small amounts of excipients

Note 1 to entry: Granulation involves agglomeration of fine particles into larger granules, typically of between 0,1 mm and 4,0 mm, depending on their subsequent use. The resulting shapes can be balls, spheroids, small cylinders or irregular.

3.9
dry granulation
granulation (3.8) without a mixing process of moistening with liquid to bind excipients and drug substances

3.10
compaction
agglomeration of *dry extracts* (3.5) and excipients without adding liquid(s) with high pressure

Note 1 to entry: Compaction uses mechanical compression or compaction (roller technic) to facilitate the agglomeration of dry powder into irregularly shaped particles.

3.11
semi-dry granulation
granulation (3.8) with a slight amount (1 % to 4 %) of granulating fluid before the granulation step

Note 1 to entry: Semi-dry granulation is a variation of the conventional wet granulation technique.

3.12
wet granulation
granulation (3.8) with a mixing process of moistening with liquid to bind excipients and drug substance followed by a drying process

3.13
first pass yield
efficiency index of a process expressed by the ratio of acceptable output to whole input obtained by a single operation

Note 1 to entry: First pass yield is a good measure of the efficiency of a process.

3.14
dosage unit
dosage amount contained in a single or daily administration

Note 1 to entry: Dosage unit of granules means minimum package unit, such as a sachet or bottle.

3.15
uniformity of dosage unit
degree of uniformity in the amount of the drug substance among dosage units

4 General requirements of manufacturing procedures

4.1 General

a) All manufacturing procedures, facilities and apparatus shall be managed under controlled conditions to ensure quality consistency between granules and traditional decoction. This document specifies general items of critical parameters in each procedure.

b) Critical parameters shall be individually verified and optimized prior to commercial production. They shall be modified according to the physical nature of the raw materials.

c) All critical parameters shall be determined by experiments in laboratories and test plants, then modified for commercial production scale. Thereafter, three lots of repetitive test production in practical production scale is required for verification study.

d) The manufacturing processes of granules shall follow the general requirements given in ISO 19617.

e) Quality testing of starting raw materials shall be conducted in accordance with the requirements given in ISO 23723. For the production and lot selection of crude drugs as starting materials, see Annex A.

f) Powder made by crushing and milling of crude drugs without extraction shall only be used in this manufacturing process instead of dry extracts if this pharmaceutical form is based on traditional usage.

g) Simple fractionation, such as two-layer partition, can be applied in the manufacturing procedure.

4.2 Crushing

a) Crude drugs shall be cut or crushed into small pieces by devices suitable for the processing of crude drugs.

b) The appropriate particle size shall be determined according to the result of equivalency evaluation (5.2).

c) In this process, the critical parameter is particle size of herbs (mm).

d) When needed, mixing usage of multiple lots of single crude drugs should be considered to avoid batch-to-batch variation and to obtain consistent quality in the final granules, as described in Annex C.

4.3 Extraction

a) Crushed drugs shall be extracted using purified water or aqueous ethanol (e.g. white wine, less than 50 % of ethanol) according to traditional methods.

b) Acidic or alkaline solvents shall not be used as extraction solvents.

c) Supercritical CO_2 gas extraction shall not be used.

d) The amount of solvent to be added is 3 to 20 times the weight of crude drugs.

NOTE This varies depending on the density and water adsorption capacity of crushed drugs.

e) Extract repetition time is set according to the result of equivalency evaluation given in Annex C.

f) Essential oils can be separately collected during the extraction process and mixed after the extraction with the obtained crude extract or sprayed on the granules or compactates.

g) In this process, the critical parameters are as follows:

1) weight of herbs or decoction pieces (kg);

2) type and amount of solvent (l);

3) extract repetition time (one to three times);

4) starting temperature (°C);

5) heat-up rising time (h);

6) temperature and holding time (°C × h);

7) pressure (Pa);

8) agitating speed or stirring speed (r/m), if equipped;

9) extraction time (h).

4.4 Liquid-solid separation

a) The extracted mixture is separated into extraction liquid and solid-phase by atmospheric or pressure filtration or (continuous) centrifugation.

b) The centrifuge machine for the separation shall be selected according to the nature of the mixture, the amount and manufacturing scale.

c) The extract yield ratio shall be evaluated by using some of the extraction liquid by drying and weighing or other appropriate analytical methods and shall be documented.

d) In this process, the critical parameters are as follows:

1) filtration process

— opening or mesh size of filter (μm);

— pressure (Pa), if applied;

2) centrifuge process

— centrifuge rotation speed (r/min)/gravity (g);

— feed temperature (°C);

— feed rate (l/h).

4.5 Concentration and drying

a) Extracted solution shall be concentrated under reduced or normal pressure at lower temperature (40 °C to 100 °C).

For batch-to-batch consistency of final product, appropriate authorized quality tests are recommended.

NOTE 1 Concentrated liquid is dried by spray or freeze dryers, belt dryer or other drying apparatus appropriate for the nature of the liquid.

NOTE 2 Intermediates (dry extracts) are obtained through concentration and drying.

NOTE 3 Different lots of dry extracts can be mixed according to the results when needed.

b) Out-of-specification lots shall not be blended with other lots for the purpose of meeting specifications.

c) Out-of-specification lots shall be stored separately from passed lots to avoid incorrect use, then discarded appropriately.

d) In this process, the critical parameters are as follows:

1) concentration process

— temperature (°C);

— vacuum (Pa);

— vapour pressure (Pa);

— solid content of concentrated liquid (%);

2) drying process by spray dryer

   — feeding liquid temperature (°C);

   — feed rate (l/h or kg/h);

   — outlet air temperature (°C);

   — atomizer rotation speed (r/min);

   — figure of atomizer disc;

3) drying process by freeze dryer

   — solid content of concentrated liquid (%);

   — vacuum (Pa);

   — shelf temperature (°C, shelf-type freeze-dryer);

   — trap temperature (°C).

4.6 Granulation

4.6.1 General

a) Intermediates (dry extracts) can be crushed to obtain a powdery substance if necessary, to homogenize with diluents, binders, disintegrants or other excipients.

b) Only authorized pharmaceutical excipients described in pharmacopoeias or other official documents shall be used.

c) The resulting powder is granulated by, for example, dry or semi-dry granulation, wet granulation or compaction.

NOTE 1 Among many excipients used for pharmaceutical products, starch, lactose, maltose, sucrose, dextrin and maltodextrin are frequently used diluents for granules or compactates made from medicinal plants. They are cost-effective and their binding abilities are generally good.

d) The particle size range of granules and compactates for herbal medicine shall be 0,18 mm to 4,0 mm.

NOTE 2 Specified particle size range varies among pharmacopoeia in each country (see Annex B).

4.6.2 Dry granulation

a) Granules can be obtained from agglomerated substance prepared by the dry granulation method.

b) Blend homogeneously extract powder and excipients such as diluents, binders, disintegrators or other authorized excipients, and then directly compress with a lubricant into agglomerates or slag tablets by appropriate technics such as a dry granulator or tableting machine.

NOTE These agglomerates or tablets are milled into granules by appropriate mill or crushing apparatus.

c) Obtained granules are sieved to give a desired range of particle sizes.

d) In this process, the critical parameters are as follows:

1) dry granulator

   — uniformity of mixing (pre-mixing time, post-mixing time, min);

   — screw rotation speed (r/m);

— rotation speed (r/m);

— roller pressure (kPa);

— temperature (°C);

2) tableting machine

— uniformity of mixing (pre-mixing time, post-mixing time, min);

— disc rotation speed (r/m);

— tableting pressure (kPa);

— temperature (°C);

e) granulation and sieving

— first pass yield (%);

— particle size distribution (μm).

4.6.3 Semi-dry granulation

a) A small amount of water or other solvents, usually less than 5 % (1 % to 4 %, preferably), is added to a mixture of dry extract powder and excipients such as diluents and binders, then mixed.

b) The moistened mixture is granulated with, for example, a device equipped with two shafts extruder and screen for classification.

c) Residual water or solvents are removed by heating to obtain dry granules.

d) In this process, the critical parameters are as follows:

1) uniformity of mixing;

2) type of solvent added and residual solvent content (%);

3) amount of solvent added (%);

4) drying temperature (°C);

5) drying duration (h);

6) residual solvents content (%);

7) water content (%);

8) particle size distribution (μm).

4.6.4 Wet granulation

a) Blend homogeneously extract powder and excipients such as diluents and binders, moisten with a solvent, form into a desired shape and size and then dry.

b) Sieve the obtained granules to give desired range of particle size.

c) In this process, the critical parameters are as follows:

1) uniformity of mixing;

2) kind of solvent added;

3) amount of solvent added (%);

4) drying temperature (°C);

5) drying duration (h);

6) particle size distribution (μm);

7) residual solvents content (%);

8) water content (%);

9) pressure (Pa).

4.7 Compaction

a) Compactates are obtained directly from the dried extract or herbal powder.

NOTE 1 Extract powder (possibly blended) and excipients such as diluents, binders, disintegrators or other authorized excipients are directly compressed with a roller compactor or a comparable technique to sheets and milled into irregular-shaped particles by an appropriate mill.

NOTE 2 These particles (compactates) are sieved to give the desired range of particle sizes.

b) In this process, the critical parameters are as follows:

1) uniformity of mixing;

2) type of excipients added;

3) rotation speed (r/m);

4) pressure (kPa);

5) temperature (°C);

6) particle size distribution (μm).

4.8 Packaging and labelling

a) Granules and compactates should be packaged into individual sachets, bags or bottles which can be tightly sealed or closed to prevent moisture.

b) Equivalency between decoction pieces and final granules or compactates shall be indicated clearly.

c) Equivalency data should be taken according to 5.2.

NOTE The following indication is an example of accurate prescription:

"1 g of this product corresponds to 3,5 g of decoction pieces or crude drugs".

d) Extraction solvent and excipients shall be correctly labelled.

The general labelling requirements specified in ISO 21371 apply.

5 General requirement of quality assurance

5.1 General

a) All tests are required for crude drugs, decoctions, intermediate (dry extracts) and final granules or compactates and a stable inherent quantity transitive relation is required.

b) Test items which do not change in the manufacturing process, such as pesticide residue and the content of heavy metals, can be omitted.

c) Assay for marker components should be conducted at each stage to obtain consistent products.

d) All the testing items and timing shall be determined based on scientific knowledge.

e) The applicable requirements for quality and safety evaluation specified in ISO 19609-1 and ISO 19609-2 apply.

5.2 Equivalency evaluation

a) Equivalency evaluation is important for final products to afford expected similar clinical effect and safety with decoction pieces or crude drugs.

b) Equivalency between dry extracts and crude drugs or decoction shall be evaluated by appropriate physicochemical parameters according to the method in Annex C.

5.3 Identification

a) One or more specific chemical component(s) in final products shall be set for identification.

b) Pattern analysis by TLC or other chromatographic methods is applicable for identification.

c) The identification method specified in ISO 19609-2 applies.

5.4 Assay

a) Content of representative chemical component(s) as quality control marker(s) is set for quality assurance.

b) A quantification test shall be conducted for starting raw materials and the final granules.

c) Additionally, a quantification test of extract solution and dry extract powder is recommended to evaluate alteration caused by each process.

NOTE Solvent extractive such as methanol is in some cases a simple and useful method to evaluate extract content included in granules and compactate (see Annex D).

5.5 Particle size and particle size distribution

a) A moderate and consistent range of particle sizes shall be set for each product.

b) The estimation of particle size and distribution shall be done by analytical sieving.

c) See Annex B for particle size of granules in the Japanese Pharmacopoeia[2], Chinese Pharmacopoeia[3], Korean Pharmacopoeia[4] and European Pharmacopoeia[5].

d) The testing method specified in ISO 19609-1 applies.

5.6 Dissolution or disintegration test

a) Granules or compactates should dissolve, disperse or disintegrate quickly in cold or hot water.

b) Appropriate tests should be conducted to evaluate these characteristics according to pharmacopoeia in each country.

c) The testing method specified in ISO 19609-1 applies.

5.7 Determination of water or moisture content

a) Water or moisture content is evaluated by mechanical methods or loss of drying under appropriate conditions.

b) Water content should be less than 8 %.

c) The testing method specified in ISO 19609-1 applies.

5.8 Uniformity of dosage units

a) To ensure the consistency of dosage units, each unit in a batch shall have a packaging amount of granules or compactates within the acceptance criteria specified in ISO 19609-1.

b) The testing method specified in ISO 19609-1 applies.

6 Requirements of safety tests

6.1 Pesticide residues

a) Appropriate residue limits of individual pesticides shall be set for granules.

b) Targets of testing pesticides should be selected according to information relating to cultivation of medicinal plants.

c) Determination of pesticide residues shall be done in accordance with ISO 22258.

6.2 Heavy metals

a) The contents of heavy metals such as arsenic, mercury, lead and cadmium shall be determined.

b) The test method specified in ISO 18664 applies.

6.3 Aflatoxins

a) The contents of aflatoxins shall be determined.

b) Determination of aflatoxins shall be done in accordance with ISO 22283.

6.4 Microorganism

a) Microbial tests shall be conducted in final granules.

b) Microbial tests in extract powder are recommended to evaluate sanitation levels of manufacturing lines.

c) Heat-resistant microorganisms should be tested in crude drugs.

d) Determination of microorganisms shall be done in accordance with ISO 22467.

Annex A
(informative)

Production, quality and selection of crude drugs

A.1 Production of crude drugs

For herbs cultivated or collected in new areas (not main production areas), the origin and species of each medicinal plant should be confirmed by not only morphological and anatomical manner but also genetically and at least with appropriate chromatographic determinations of the minimum amounts of marker constituents or a typical fingerprint as described in ISO 19609-2. Morphological evaluation of the parts other than medicinal parts sometimes provides important information for identifying species when no reliable genetic database exists. Therefore, flowering season is a good time for identifying herbs. Raw herbs must be processed after harvest in the traditional manner.

A.2 Requirements for crude drugs

Various quality tests should be conducted for crude drugs as starting materials of medicinal products. Test items and methods should refer to ISO 23723.

A.3 General attentions to select crude drug lots

Crude drugs with no or small lot-to-lot variation can be used as starting materials without further investigation. However, some herbs have large lot-to-lot variation. In such cases, multiple lots should be blended based on the reliable analytical data to obtain consistent final products. Appropriate sampling points and amounts shall be designed to obtain a representative average value of the lot according to the characteristics of each herb.

Annex B
(informative)

Particle size distribution

Table B.1 — Particle size distribution of granules in pharmacopoeias

Pharmacopoeia	Sieve mesh size µm	Remain %
CP	2 000 ± 70 to 180 ± 7,6	≥ 85
KP	1 700	0
	1 400 to 1 700	< 5
	355 to 1 400	≥ 85
JP	Not specified[a]	
EP	Not specified[a]	

Key

CP Chinese Pharmacopoeia

EP European Pharmacopoeia

JP Japanese Pharmacopoeia

KP Korean Pharmacopoeia

[a] In the Japanese Pharmacopoeia and the harmonized European Pharmacopoeia, formulation with a granulation process is defined as granules and no particle size distribution range is specified.

Annex C
(informative)

Equivalency evaluation

C.1 General

Equivalency should be evaluated by comparison of extract from standard decoction and semi or full scale of practical manufacturing apparatus. Whole dry extract yield and extract rate of marker components are the main parameters for evaluation. In addition, whole chromatographical fingerprint comparison by high-performance liquid chromatography (HPLC) equipped with a UV or photo-diode array (PDA) detector or the liquid chromatography-mass spectrometry (LC-MS) technique provides information on qualitative equivalency. Since the nature of medicinal plants can change gradually, periodical quality re-evaluation is recommended.

C.2 Samples

Prepare three lots of a sufficient amount of theoretically necessary crude drugs which meet pharmacopoeia or regional requirements for this evaluation. All the crude drug lots should be obtained from districts which will be used as future cultivation or collection area(s) for commercial manufacturing.

C.3 Example of lot combination for multiple medicinal plants formulation (in case of five crude drugs)

Randomly select one lot of each crude drug from three lots. Thereafter, make three combined lots consisting of one lot each of crude drug as in Table C.1. The same corresponding combination lots shall be used in the preparation of both standard decoction and dry extract.

Table C.1 — Crude drug lots

Crude drug A	Crude drug B	Crude drug C	Crude drug D	Crude drug E
lot 1	lot 1	lot 1	lot 1	lot 1
lot 2	lot 2	lot 2	lot 2	lot 2
lot 3	lot 3	lot 3	lot 3	lot 3

Combined lot 1: A-1, B-2, C-3, D-1, E-2

Combined lot 2: A-2, B-3, C-1, D-2, E-3

Combined lot 3: A-3, B-1, C-2, D-3, E-1

C.4 Standard decoction

Prepare standard decoctions with three lots of 100 g to 200 g of crude drugs by traditional ware such as a clay pot in a traditional manner, such as particle size of herbs, solvent amount and temperature, extraction times and repetition times. Extracted fluid is filtered by paper or cloth or decanted according to a traditional method. The whole or part of the filtrate is lyophilized directly or after concentrating. Experiments shall be repeated three times for each lot.