FINAL
DRAFT

INTERNATIONAL
STANDARD

**ISO/FDIS
23419**

ISO/TC **249**

Secretariat: SAC

Voting begins on:
2021-09-06

Voting terminates on:
2021-11-01

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

Reference number
ISO/FDIS 23419:2021(E)

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Published in Switzerland

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Foreword

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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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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/FDIS 22467,[1)] *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 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 https://www.electropedia.org/

1) Under preparation. Stage at the time of publication: ISO/FDIS 22467:2021.

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 (%);