International Standard

ISO 8284

Traditional Chinese medicine — Simplified accelerated stress simulation methods

Médecine traditionnelle chinoise — Méthodes simplifiées de simulation accélérée des contraintes

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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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.

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Introduction

Stability is the most important quality criterion for pharmaceutical products after production. So typically for all pharmaceutical products an accurate expiry date is established based on scientific measurement data. In addition to long-term storage tests, accelerated stability tests under specific stress conditions can be carried out at the same time in order to reproduce possible degradation reactions. The aim of the stability tests should be to obtain the most accurate possible assessment of the effects of packaging, closure, dosage, batch, temperature, humidity, pH value and light, as well as other potential factors influencing decomposition processes.

Phytopharmaceuticals are substances from plants, plant parts and plant components in processed or unprocessed condition. Like all other medicinal products, they are subject to authorisation; and the quality, efficacy and harmlessness of the respective preparations must be demonstrated. In contrast to chemically defined drugs, the active ingredient of a phytopharmaceutical is not a single substance, but usually an extract.

The extract as a whole is regarded as the active substance. Depending on the state of knowledge on the active principle of medicinal plants, extracts can be classified as follows:

— extracts for which the efficacy-determining ingredients are known and for which a clear dose-response relationship can be established (e.g. anthraquinone drugs);

— extracts for which co-efficacy-determining ingredients are known, but other (possibly unknown) ingredients are responsible for the overall effect (e.g. St. John's wort);

— extracts which show pharmacological effects but for which the effect cannot be assigned to specific substances.

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All pharmaceutical manufacturers must guarantee the consistent, high quality of their products in the whole shelf life. According to international health laws, quality means the nature of a drug, which is determined by the identity, content, purity and other chemical, physical and biological properties or by the manufacturing process as well as the stability.

Herbal medicinal products in the sense of rational therapy are regarded as real remedies. In this respect, the same legal requirements regarding efficacy and harmlessness apply as for chemically defined substances. Nevertheless, there are significant differences in the composition of the two forms of medicine. While chemically defined substances are usually considered as single substances or combinations of a few substances, herbal medicinal products are highly complex multi-component mixtures with hundreds of ingredients. Therefore, a much greater analytical effort is required to satisfy the qualitative demands on the finished product.

According to the national and international requirements on the quality of herbal medicinal products, the drug or the single herbal finished product as a whole is regarded as the active substance to be investigated. National or international guidelines for new or existing active substances and final products are taken into consideration in the process of stability control. However typically the guidelines already indicate that they are not intended to apply for biologically or biotechnologically manufactured medicinal products; and the guidelines do not take into account the specificities of herbal medicinal products.

Quantitative studies of the content of efficacy-determining ingredients ensure, that under defined storage conditions there are no changes in content of typically more than ±5 % compared to the initial value over the proposed shelf life. If no defined active substances are present, a deviation of ±10 % from the content of main substances can be accepted. Other "significant changes" mentioned in the guidelines are changes in pH value, solubility and appearance which would lead to a failure of the approval.

The stability of a few ingredients is the basis for the stability of the whole herbal preparation.

To monitor the qualitative and quantitative composition, high pressure liquid chromatography (HPLC) with ultra violet (UV)-diode array detection is mostly used, because the highest measurement accuracy can be expected from this method. In addition, the extracts are examined by thin layer chromatography (TLC) with various mobile phase systems as a further fingerprint method for qualitative changes in the ingredient

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spectrum. In order to avoid the problem of repeatability in TLC, the samples should not be measured immediately but should be collected as deep-frozen samples.

In addition to the monitoring of the ingredients by chromatographic methods, the physical changes of the drugs and extracts should also be documented at the respective sampling times. Other quality features include a change in appearance and organoleptically measurable changes.

International regulations define the framework conditions for accelerated stress simulation without making detailed proposals for its realization in the laboratory.

This document defines simple and detailed methods for the technical implementation of the required stability tests.

NOTE Stress testing of the active substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability and validate the stability indicating power of the analytical procedures used.

When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures.

Since the herbal substance or herbal preparation in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity does not suffice. The stability of other substances present in the herbal substance or in the herbal preparation should, as far as possible, also be demonstrated, for example, by means of appropriate fingerprint chromatograms. It should also be demonstrated that their proportional content remains comparable to the initial fingerprint. If a herbal medicinal product contains combinations of several herbal substances or herbal preparations, and if it is not possible to determine the stability of each active substance, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay and physical and sensory tests or other appropriate tests.

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Traditional Chinese medicine — Simplified accelerated stress simulation methods

1 Scope

This document specifies the application of simplified accelerated stress simulation methods for stress tests of finished products, used in and as Traditional Chinese medicine (TCM). Testing for stability or degradation under the influence of daylight or sunlight is outside the scope of this document.

2 Normative references

There are no normative references in this document.

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/

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3.1
accelerated stress simulation
exaggerated conditions, such as gas, chemical and storage, to increase the rate of chemical degradation or physical change of a product

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3.2
centrifuge tube with plug seal screw cap
standardized plastic test tube with a screw top cap

3.3
fermenting tube
fermentation tube
glass tube with two spheres, which allows the escape of emerging gas and prevents entering of ambient air into a closed system

3.4
marker compound
chemical constituent that can be used to verify the potency or identity of a medicinal product

3.5
out-of-specification
OOS
examination, measurement or test result that does not comply with defined acceptance criteria

[SOURCE: ISO 22716:2007, 2.21, modified — The abbreviated term "OOS" has been added.]

3.6
SPE cartridge
short column (generally an open syringe barrel) containing porous metal or plastic frits

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4 Simplified accelerated stress simulation methods

4.1 General

Drug stability and the course of changes in a product from manufacture to consumption by the patient are critical parameters in the product development. So far, only theoretical mathematical relationships or experimental test series for the simulation of longer storage conditions exist.

Valid test procedures therefore must be critically questioned as to whether they can also be applied over the entire stability period – usually 36 months. The test procedures shall coincide with those of the approval or registration procedure and cannot simply be subsequently adapted to any changed external conditions. If the products do not meet the stability criteria, i.e. out-of-specification (OOS) results occur in the testing laboratory, the causes for this shall be identified and risk assessment processes shall be established.

It is therefore imperative to make appropriate stability predictions by means of a bundle of analytical investigations and simulated stress conditions, without additionally extending the often long development process by the prescribed 36 months.

It is therefore necessary to establish a cost-effective and fast simulation for finished products with a relatively large chance of being able to make a realistic stability prediction by suitable accelerated stress simulations. This proves to be an obstacle that is difficult to overcome, especially in the case of herbal preparations, since the concrete active substance in the chemical sense is often not known in comparison to the chemically defined active substance in synthetic preparations. The mechanism of action of herbal extracts is usually known, so analytics shall be focused on one or more meaningful lead substances (marker compounds). To ensure the reliability of the results, each test approach should be carried out with three parallel test samples.

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4.2 Different types of accelerated stress simulation

4.2.1 Types of accelerated stress

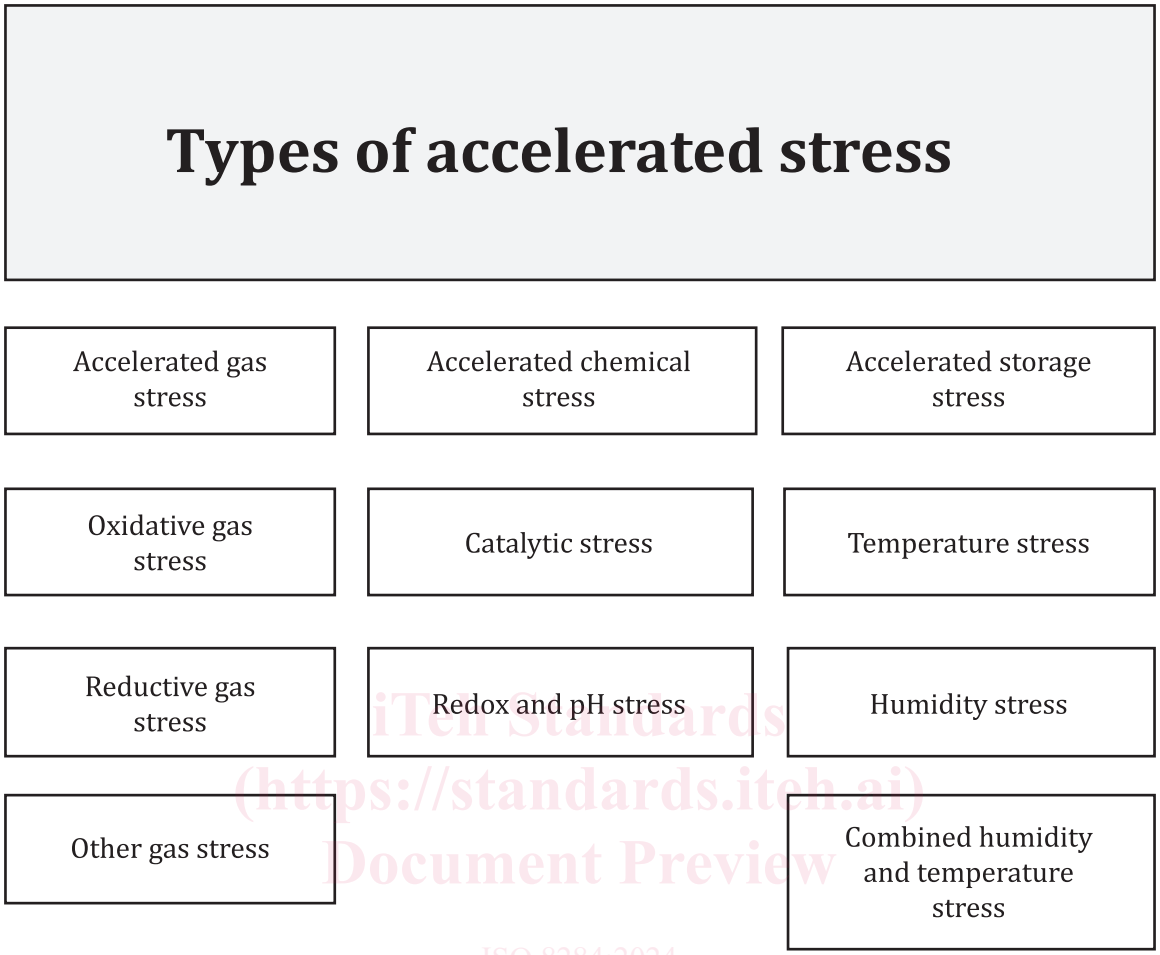

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Figure 1 — Types of accelerated stress

4.2.2 Accelerated gas stress simulation

Typical gas stress can be generated by:

— oxidative gases;

— reductive gases;

— other types of reactive gases.

Accelerated gas stress simulation should be used to assess the influence of these gases on the stability of finished products (see Figure 1 column 1).

For validation of the proposed test setup, an accuracy criterion is described in Annex A.

4.2.3 Accelerated chemical stress simulation

Typical chemical stress can be generated by:

— catalytic constituents;

— compounds with a specific redox potential;

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