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Guideline for Self-Stability Study on Plastic and Rubber Pharmaceutical Packaging Materials

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Foreword

This standard is drafted in accordance with the rules given in the GB/T 1.1-2020 Directives for standardization - Part 1: Rules for the structure and drafting of standardizing documents.

Attention is drawn to the possibility that some of the elements of this standard may be the subject of patent rights. China National Pharmaceutical Packaging Association shall not be held responsible for identifying any or all such patent rights.

This standard was proposed by and is under the jurisdiction of China National Pharmaceutical Packaging Association.

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Introduction

The self-stability study on pharmaceutical packaging materials is designed to investigate change rule of the packaging materials and containers in direct contact with drugs (hereinafter referred to as pharmaceutical packaging materials) over the time under specified temperature and humidity environment so that scientific basis can be established for storage conditions and expiration date of pharmaceutical packaging materials combination with drugs determined by drug manufactures.

Self-stability study on pharmaceutical packaging materials is generally conducted by manufacturers of pharmaceutical packaging materials to confirm the time limit of stable quality of the product under the specified storage conditions, which is an important factor to be considered by pharmaceutical manufacturers to select pharmaceutical packaging materials to conduct suitability evaluation and which is also helpful to guide pharmaceutical manufacturers to store, transport and use pharmaceutical packaging materials under specified conditions. The time limit of stable quality of the pharmaceutical packaging materials refers to the time limit of stability of the pharmaceutical packaging materials from the production date of pharmaceutical packaging material to the end of shelf life of drugs. The time limit shall be a period when the quality characteristics of pharmaceutical packaging materials are expected to be guaranteed under the prescribed conditions or under the prescribed conditions of storage.

Pharmaceutical packaging materials can be classified into various categories (General Rule <9621>, Vol IV, Edition 2020 of Chinese Pharmacopoeia) according to the material and risk degree. As far as the materials are concerned, some products used in pharmaceutical packaging have aroused wide concern both at home and abroad due to the fact that their materials may be affected by environmental factors resulting in stability problems like aging, especially those plastic and rubber products widely used in pharmaceutical packaging field. Moreover, this kind of high polymer products is the main raw material or component used in the majority of pharmaceutical packaging materials with high risk. Stability issue of pharmaceutical packaging materials can, on the one hand, cause pharmaceutical packaging materials to lose their protection and functional performance, thus indirectly affecting the safety of drugs in clinical use, and on the other hand, the ageing of the materials and finished products may result in changes in extractables and potential leachables. Therefore, stability study on pharmaceutical packaging materials is not only conducive to providing basis to help manufacturers of pharmaceutical packaging materials to verify and validate reasonable formula, design of processing technology and the time limit of quality stability, but also of important guiding significance to pharmaceutical manufacturers to select and reasonably use pharmaceutical packaging materials according to the properties of the preparations.

This standard is based on the quality standard and process of pharmaceutical packaging materials approved and marketed in our country, for technical guidance only, and applicability of this standard should be considered for other special materials and process products.

Guideline for Self-Stability Study on Plastic and Rubber Pharmaceutical Packaging Materials

1 Scope

This standard stipulates the study method of self-stability of plastic and rubber pharmaceutical packaging materials.

This standard is applicable to the self-stability study of plastic and rubber pharmaceutical packaging materials. For the functional outer bag not in direct contact with the drug, it can be implemented by referring to this standard.

2 Normative References

There are no normative references in this standard.

3 Terms and definitions

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

3.1 The time limit of stable quality

The time limit of stability of the pharmaceutical packaging materials from the production date of pharmaceutical packaging material to the end of shelf life of drugs. The time limit shall be a period when the quality characteristics of pharmaceutical packaging materials are expected to be guaranteed under the prescribed conditions or under the prescribed conditions of storage.

3.2 Accelerating test

The sample is stored at a higher temperature to shorten the time to simulate the actual time of aging test.

3.3 Long-term test

Long-term test is to be conducted under nearly actual storage conditions for pharmaceutical packaging materials, intended to provide real basis for study results of accelerating test and provide support for establishing the time limit of quality stability of pharmaceutical packaging materials.

4 Stability study

4.1 Basic requirements

Prior to stability study on pharmaceutical packaging materials, literature related to materials and technology of the pharmaceutical packaging shall be referred to, through which the impact of environmental conditions like temperature, humidity, illumination, oxidation, peroxide, ozone, irradiation, etc. on materials and finished products can be understood. Generally, basic requirements for stability study on pharmaceutical packaging materials include the following aspects:

a) Stability study consists of study of influence factors, accelerating test and long-term test. If study of influence factors is to be conducted, at least one batch (including one batch) of samples shall be required. At least one batch (including one batch) of samples shall be required in accelerating test and long-term test.

b) Samples used in stability study shall be representative. Samples used in stability study generally come from stable production line and mass production, whose product formulation, production process, product specification and packaging shall be in consistent with those of products in commercialized production. Quality standard of the samples shall be in consistent with that of products from mass production.

c) Data from long-term test are final basis for establishing the time limit of stable quality of pharmaceutical packaging materials.

d) As far as packaging container system is concerned, the time limit of stability of the packaging container system shall be validated based on comprehensive consideration of the time limit of each component. If there are differences among time limits of packaging components, the shortest time limit of stability is generally taken as the stable period of the packaging container system.

4.2 Evaluation considerations

4.2.1 Study of influence factors

The study is to explore the factors affecting the stability of pharmaceutical packaging materials and possible degradation pathways, providing scientific basis for the processing, packaging, and storage conditions of pharmaceutical packaging products. The factors that are taken into consideration in study of influence factors generally include temperature, humidity, illumination, oxidation, peroxide, ozone, irradiation, and so on. Literature research is the first choice for the study of influencing factors. If literature research is not sufficient, study of influence factors can be conducted on at least one batch (including one batch) of samples by referring to study model of influence factors for plastic or rubber materials or products or by referring to the study model from authoritative literature published both at home and abroad.

4.2.2 Accelerating test

The test is conducted under accelerated conditions, intending to evaluate the stability of pharmaceutical packaging materials by accelerating aging of pharmaceutical packaging materials to provide necessary data for establishment of design, use, packaging, transportation, storage and stable period of pharmaceutical packaging material.

At least one batch of test samples are required, which shall be packaged with commercially available manner or equivalent to commercially available manner and will be stored under the selected temperature and humidity till necessary accelerated aging time. The devices used in the accelerated aging test shall be able to control the temperature ±2℃ and relative humidity ± 5% and shall be able to perform real-time monitoring and automatic recording for real temperature and humidity.

The method of accelerated aging factor is simple and strict technique to study the long-term effect of pharmaceutical packaging materials, and accelerating test shall be conducted along with long-term test at the

same time. See Annex A for detailed information about theory of accelerated aging and determination of parameters.

4.2.3 **Long-term test**

Long-term test is to be conducted under nearly actual storage conditions for pharmaceutical packaging materials, intended to provide real basis for study results of accelerating test and provide support for establishing the time limit of quality stability of pharmaceutical packaging materials.

At least one batch of test samples with commercially marketing package or equivalent to commercially marketing package are stored at 25℃±2 ℃ and with RH of 60%±10% till expected stable period (for example, no less than 3 years). It's suggested that the test samples are sampled every six months (including Time zero), and tests to be conducted according to items of stability. A comprehensive assessment is conducted on the measurement results to determine the time limit of stable quality of the pharmaceutical packaging materials by using the proposed quality standards or guidelines, approved or prescribed quality standards.

For the pharmaceutical packaging material expected to package the drug which needs refrigeration, the samples going through conditions of long-term test shall be stored at 25℃±2 ℃ and with relative humidity of 60%±10% (for example, at least one year), followed by storage at 5℃±3 ℃for 2 years. The test shall be conducted according to the above-mentioned time requirements to determine the stable period for the pharmaceutical packaging materials to package the drug which needs refrigeration.

For the pharmaceutical packaging material expected to package the drug which needs frozen, the samples going through conditions of long-term test shall be stored at 25℃±2 ℃ and with relative humidity of 60%±10% (for example, at least one year), followed by storage at -20℃±5℃ for two years. The test shall be conducted according to the above-mentioned time requirements to determine the stable period for the pharmaceutical packaging materials to package the drug which needs frozen.

For the pharmaceutical packaging material expected to package the drug which will be stored at other temperature conditions, the samples going through conditions of long-term test shall be stored at 25℃±2 ℃ and with relative humidity of 60%±10% (for example, at least one year), followed by storage at the temperature required for corresponding drug for two years. The test shall be conducted according to the above-mentioned time requirements to determine the stable period for the pharmaceutical packaging materials used in other storage conditions.

Note: if the validity period for the drug stored at cold storage, refrigeration, or other temperatures for over two years, the drug shall be stored at the cold storage, refrigeration, or other temperatures for required period.

5 **Inspection Items**

5.1 **General considerations**

Inspection items for stability of pharmaceutical packaging material shall generally meet the technical requirements of the product, such as requirements in *Chinese Pharmacopoeia*, *National Standards for Pharmaceutical Packaging Materials* or manufacturer's registration standard of the product. When selecting the actual inspection items, the investigators can refer to the purpose and meaning of different items in the standards to determine whether accelerating test or long-term test will exert impact on the pharmaceutical packaging materials or determine whether the test is of significance for inspection after accelerating test or long-term test. In addition, according to the concept of biological research and the principle of animal conservation, the product required to go through biological test may be tested only at 0 month of the stability test and at the final time point to determine that the pharmaceutical packaging material still has sufficient safety at the end of the stable period. As for inspection items for stability, in addition to considering adopting *National Standards for Pharmaceutical Packaging Materials* and manufacturer's registration standards, appropriate relevant test items outside the standards shall also be taken into consideration according to different material properties and processing technology properties of products. Moreover, due to the fact that protectiveness, functionality and safety have been given more considerations in setting quality control items and indexes for standards of the pharmaceutical packaging materials, besides considering the above factors, inspection factors related to degradation shall also be taken into consideration and see Table 1 for items for reference.

Table 1 Reference Examples of Other Inspection Items Related to Degradation

Items	Examples of focus of inspection or concern
Appearance	Changes in color and glossiness, and cracks
Tensile strength test	Changes in tensile strength, elongation at break
Thermoanalysis of differential scanning calorimetry	Glass transition temperature (Tg) and change in thermal enthalpy value
Infrared spectrometry	1710-1740cm^{-1} nearby characteristic peaks and their changes
Observation through microscope or scanning electron microscope	Changes in surface characteristics
Antioxidant	Changes in contents of antioxidant

For the pharmaceutical packaging materials provided sterile, its packaging design should be able to maintain its seal strength and packaging integrity before filling to prove retention of the sterility state.

For the pharmaceutical packaging materials composed of layers like products with film coated rubber closure, multi-layer co-extrusion products, composite film products or some coating products, etc., it is also necessary to prove that the stability of multi-layer structure can be maintained during the stable period or its change is acceptable. See Table 2 for items reference. It should be noted that there are generally lack of general accepted criteria for inspecting structural stability of products with multilayer structures, and the stability of some products is not necessarily unacceptable even though there are some slight changes. Therefore, in application of this guideline, it is necessary to consider and discuss the acceptability of stability of products with multilayer structures according to the specific application of the product and the comprehensive research data.

Comprehensive analysis and assessment shall be conducted on the data from stability test to make conclusions for stability study of pharmaceutical packaging materials.

Table 2 Reference Examples of Product Structure Stability Inspection of Pharmaceutical Packaging Materials Composed of Multilayered Structures

Items	Examples of focus of inspection or concern
Appearance	Folds, changes in color and layers
Observation through scanning electron microscope	Changes in multilayer structure, including whether there is breakage; electronic microscope observation of cross section after folding-and-unfolding of multilayer film at 180°
Tensile strength test	Whether the cross section has layered
Adhesion of coating	Scraping test
Peel strength	Changes in peel strength of composite product

5.2 Inspection items

See Table 3 for inspection items of major categories of pharmaceutical packaging materials, and for the items and categories not listed in Table 3, inspection items can be determined based on variety of the pharmaceutical packaging materials.

Table 3 Reference List for Inspection Items of Products Made from Plastic and Rubber Pharmaceutical Packaging Materials

Drug form to be packaged		Investigation items for functionality and protectiveness	Investigation items for stability
Injections	Plastic	Appearance, microscopic features*, thermal adaptability, resistance to dropping, light transmittance, puncture force*, retainability of puncture outfit and impermeability at the insertion point, sealability, suspension force*, gas transmission, tensile strength, thermal sealing strength, opening force of pull ring*, thermoanalysis	Insoluble particles*, extraction test (clarity and color, pH value, absorbance, readily oxidizable substance)
	Rubber	Appearance, penetration force*, integrity, sealability, thermoanalysis	Fragmentation from puncture, insoluble particles*, chemical properties (clarity and color, absorbance, readily oxidizable substance)
Spray (aerosol)		Appearance, dimensions*, patency*, sealability, pressure resistance, pulling-out force*, pressure-disengaging force*, discharge rate error	Extraction test (clarity and color, pH value, absorbance, readily oxidizable substance), coating quality, microbial limit*
Eye drops		Appearance, sealability, dropping amount*, thermoanalysis,	Visible foreign matter*, Extraction test (clarity, pH value, absorbance, readily oxidizable substance), n-hexane nonvolatile matter, decolorization test, sterility* (If applicable, a validated packaging system integrity evaluation method can also be used.)
Paste (pasta, gel and patch)		Appearance, pressure-resistant strength, peel strength, tensile strength, thermal sealing strength, sealability, gas transmission, ethyl alcohol transmission*, oil-penetrating property*, thermoanalysis	Extraction test (clarity, pH value, absorbance, readily oxidizable substance), microbial limit*, sterility* (If applicable, a validated packaging system integrity evaluation method can also be used.)
External liquid preparation		Appearance, sealability, resistance to dropping*, gas transmission, ethyl alcohol transmission *, oil-penetrating property*, thermoanalysis	Extraction test (clarity and color, pH value, absorbance, readily oxidizable substance, n-hexane nonvolatile matter), decolorization test, microbial limit*, sterility* (If applicable, a validated packaging system integrity evaluation method can also be used.)
Suppository		Appearance, sealability, gas transmission, tensile strength, peel strength, thermal sealing strength, thermoanalysis	Extraction test (readily oxidizable substance, n-hexane nonvolatile matter), microbial limit*, sterility* (If applicable, a validated packaging system integrity evaluation method can also be used.)
Oral dosage		Appearance, sealability, resistance to dropping*, vibration test*, gas transmission, tensile strength, peel strength, thermal sealing strength, thermoanalysis	Extraction test (readily oxidizable substance, n-hexane nonvolatile matter), decolorization test, microbial limit*
Active pharmaceutical ingredients		Appearance, gas transmission, tensile strength, elongation at break, thermal sealing strength, thermoanalysis	Extraction test (readily oxidizable substance, n-hexane nonvolatile matter)

Note 1: Inspection items may not be limited to those listed in Table 1 or can be selected based on the preparations to be used.
Note 2: The *item is optional, and the user of this guideline decides whether to investigate them by taking properties, intended use of pharmaceutical packaging material and other factors into consideration.

Annex A
（informative）
Theories of Accelerated Aging and Determination of Parameters

Accelerated aging means that the safety and function of materials or finished products change over time. The accelerated aging technique is based on the assumption that the chemical reaction contained in the degradation follows the Arrhenius reaction velocity function which indicates that the rate of chemical reaction will be approximately doubled or reduced by half (Q_{10}) with temperature increasing or decreasing by 10℃ in the same process. The steps for accelerating test are as follows:

A.1 Material and product characterization

The accelerated aging theory and its application are directly related to the composition of pharmaceutical packaging materials. Material characteristics that may affect the results of accelerated aging include: composition; morphology [glassy state, amorphous, semi-crystal, high crystal, % crystal, etc.; thermal conversion (material melting temperature (Tm), glass transition temperature (Tg), alpha temperature (Tα))]; additives, processing aids, catalysts, lubricants, residual solvents, corrosive gases and fillers. Thermal transition temperature (Tm, Tg, Tα) of pharmaceutical packaging materials needs to be taken into consideration in selecting accelerated aging temperature (TAA), and the aging temperature should be lower than any conversion temperature of the pharmaceutical packaging materials and lower than the temperature that causes pharmaceutical packaging material to distort. The investigator should collect above information about the test sample materials.

A.2 Steps of accelerated aging protocol

A.2.1 Temperature and time function used in accelerated aging refer to equation A.1 and equation A.2.

$$AAF = Q_{10}^{[(T_{AA}-T_{RT})/10]} \quad \text{.....(A. 1)}$$

$$AAT = \frac{\text{Desired(RT)}}{AAF} \quad \text{.....(A. 2)}$$

AAF —— Accelerated aging factor, which is a calculated or estimated time ratio of the actual storage conditions of pharmaceutical packaging material up to the same level of performance changes.

Q_{10} —— it refers to the aging factor when the temperature increases or decreases by 10℃.

T_{AA} —— it refers to a certain higher temperature used in study of aging. It is calculated based on the estimated storage temperature.

AAT —— it refers to the time span of accelerated aging test.

T_{RT} —— refers to the storage temperature at the time of the actual aging sample, which represents the actual storage conditions.

Desired (RT) —— expected period of validity.

A.2.2 **Steps of accelerated aging protocol**

A.2.2.1 **Select the aging factor Q_{10} value**

Q_{10} = 2 is the conservative value of the aging factor that is generally used. More radical reaction rate factor can also be used (for example, Q_{10} = 2.2-2.5), but the packaging material to be studied must have good literature representation in terms of aging rate.

The explicitly expected time limit of stability of pharmaceutical packaging material on the basis of the market demand, product demand and other aspects. Determine room temperature or ambient temperature (T_{RT}) and the accelerated aging temperature (T_{AA}).

Room temperature or ambient temperature (T_{RT}) has been determined to be 25℃ based on long-term test parameters. Accelerated aging temperature (T_{AA}): select appropriate accelerated aging temperature based on the properties of the materials that pharmaceutical packaging material used. It is recommended to use temperature no higher than 60℃. A long-term test is only conducted when the material characterization indicates that aging conducted by the increase of temperature is not feasible.

A.2.2.2 **Calculate the test cycle with Q_{10}, T_{RT} and T_{AA}**

Determine the time interval of aging test, including zero time, generally no less than five times. For example, when accelerated aging temperature 60℃ is used (Q_{10} = 2), the desired stable period is 5 years, and it is necessary to sample at 32 days, 65 days, 97 days, 129 days and 161 days, and item test shall be conducted according to stability.

A.2.2.3 **Determine the relative humidity (RH) condition**

Physical and chemical calculator can be used to calculate the relative humidity based on the corresponding amount of water vapor under different temperatures. According to the parameters for long-term test, when it is at 25℃, the moisture concentration under the relative humidity of 60% is 15 128×10^{-6}, so that the corresponding relative humidity under other temperature can be calculated.

Examples of accelerating test conditions are as follows (room temperature at 25℃, relative humidity 60%, Q_{10}=2):

Table A.1 Example of Accelerating Test Conditions

Expected period of validity (yr)	Accelerated aging temperature (℃)	Relative humidity (%)	Test cycle (day)
3	60	10	96
	50	15	193
	40	26	387
	30	45	774
5	60	10	161
	50	15	322
	40	26	645
	30	45	1290

Addition of humidity parameter in the aging protocol is not expected to assess the effect of humidity on packaging materials. If this aspect of evaluation is required, independent non-aging protocol including the determined humidity limit in advance should be adopted.

The figure A.1 shows an example of the concentration of water in the air as a function of temperature and relative humidity.

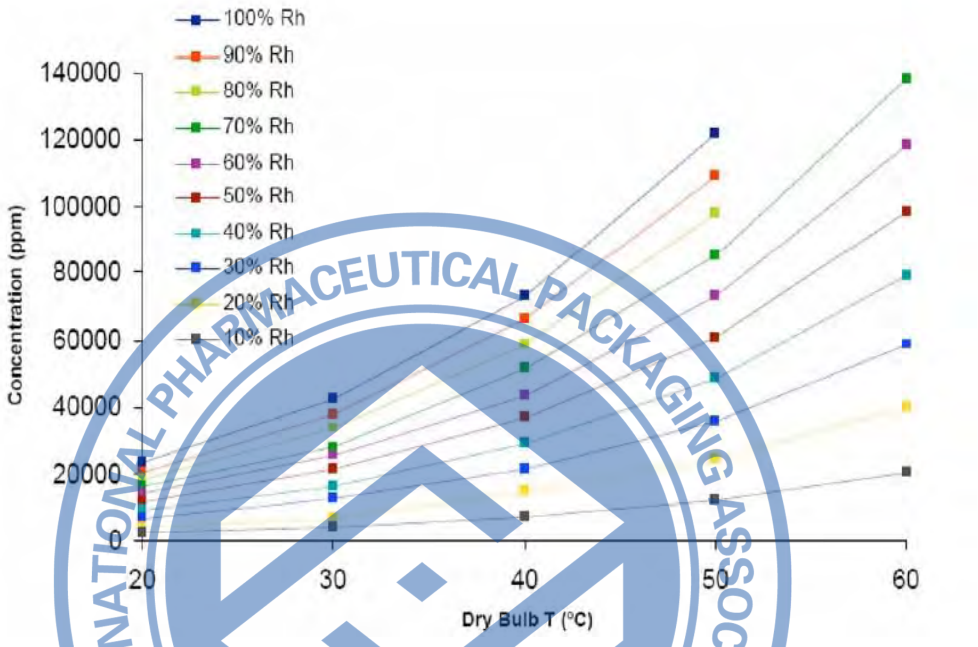

Fig A.1 Examples of the concentration of water in the air as a function of temperature and relative humidity

Table A.2 shows examples of relations between relative humidity and constant moisture content under different temperature conditions.

Table A.2 Examples of Relations between Relative Humidity and Constant Moisture Content under Different Temperature Conditions

Temperature (℃)	Relative Humidity (%)	Water Content
23	50.0	13 750×10^{-6}
40	19.1	13 750×10^{-6}
50	11.4	13 750×10^{-6}
55	9.0	13 750×10^{-6}
60	7.1	13 750×10^{-6}

References

[1] GB/T 19633.1-2015 Packaging for Terminally Sterilized Medical Devices - Part 1: Requirements for Materials, Sterile Barrier Systems and Packaging Systems (ISO 11607-1:2006)

[2] YY/T 0681.1-2018 Test Method for Packaging of Sterile Medical Devices - Part 1: Accelerated Aging Test Guidance

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[4] Chinese Pharmacopoeia 9001 Guideline for Stability Study of Active Pharmaceutical Ingredients and Drug Products.

[5] NMPA Technical Guideline for Stability Study of Chemical Drugs (active pharmaceutical Ingredients and drug products).

[6] ICH Q1A (R2) Stability Testing of New Drug Substances and Products