MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

GENERAL PHARMACOPOEIA MONOGRAPH

Shelf lives of medicinal products

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The requirements of this general article apply to methods for determining the stability of commercially manufactured medicinal products, which underlie determination of their shelf lives.

Basic terms and definitions

Shelf life is a period, during which a medicinal product completely meets all the requirements of the normative documentation, in accordance with which it was manufactured and stored.

Stability is the ability of a medicinal product to preserve its chemical, physical, microbiological, biopharmaceutical and pharmacological properties within certain limits during its shelf life.

Long-term stability studies are tests conducted in accordance with the claimed storage conditions of the medicinal product, specified in the normative documentation, in order to determine or confirm its shelf life.

Accelerated stability studies are tests conducted at elevated temperature in order to determine or confirm the shelf life of a medicinal product.

Stress stability studies are stability tests under stress conditions, conducted to investigate the forced degradation process (determination of degradation products and mechanisms) of a medicinal product.

Matrixing is a study method that tests only a subgroup from the total number of samples of all combinations of factors to be tested at a certain time point.

Bracketing is a stability study method that tests only samples with extreme

variants of factors at all time points using a full protocol.

Extrapolation is a method to obtain information on future data based on the available ones.

Date of manufacture of medicinal products is a date of the first manufacturing operation related to mixing of an active pharmaceutical ingredient with other components. For active pharmaceutical ingredients, the date of manufacture is the initial date of filling and packaging operations.

Release date is a date of the medicinal product release or the approval of its release in circulation.

General provisions

The shelf life of a medicinal product is established experimentally during its storage for a certain period under conditions and in a package specified in the normative documentation. As the data is accumulated, it can be both increased and decreased.

Determination of a shelf life is based on a drug stability study using chemical and physicochemical analytical methods specified in general pharmacopoeial articles, as well as, if necessary, other specific study methods, for example, biological methods, pharmacological tests.

The shelf-life of a medicinal product is determined irrespective of the shelf lives of active pharmaceutical ingredients. However, for medicinal products produced by packaging active pharmaceutical ingredients, it should be considered that stability of medicinal products may depend on the remaining shelf life of the active pharmaceutical ingredient used.

The residual shelf life means the period of time remaining until the end of the specified shelf life of the medicinal product.

It should be also taken into account how the stability of medicinal products is affected by long-term storage of bulk and intermediate products before their transfer from one production area to another or to the packaging area.

The initial shelf life of a medicinal product is determined by the manufacturer (developer) of the medicinal product when preparing the draft

normative documentation.

After the medicinal product is registered and its commercial-scale manufacture is started, the manufacturer (developer) must continue stability studies of the medicinal product in order to confirm or adjust its shelf life.

Shelf lives over 5 years are not recommended for medicinal products, even if the stability study results justify this.

Any changes in shelf lives or storage conditions of medicinal products should be approved pursuant to the established procedure, based on the data confirming the validity of the proposed changes.

The expiration date of a commercial batch of a medicinal product is determined from the date of issue of the permit for its marketing (release date). Under normal circumstances, the period to the date of issue of such a permit should not exceed 30 days from the date of manufacture.

If the permit for marketing of a medicinal product batch is issued after the established 30 days from the date of manufacture, the date of manufacture should be assumed the start of the medicinal product shelf life.

This approach is not applicable for immunobiological medicinal products, such as vaccines, serums, toxins and allergens, for drugs derived from human and animal blood and plasma, as well as for drugs produced using biotechnological processes and methods.

The optimum requirements for primary and secondary packaging and storage conditions are determined based on studies of the medicinal product properties.

After determining the optimal requirements for primary and secondary packaging and storage conditions, the manufacturer (developer) of the medicinal product experimentally determines its shelf life by storing the product in the recommended package and under the specified conditions in order to detect any hidden factors that may affect the product stability during its storage. For this purpose, a sample from each of at least 3 batches of the medicinal product specially produced according to laboratory or pilot manufacturing specifications,

should be selected and packaged in an amount sufficient to study the medicinal product stability.

When studying the stability of medicinal products packaged in large-sized primary packaging (jars, carboys, iron drums, tin drums, polymer bags, three- and four-layer paper bags, etc.), a similar package with a smaller volume sufficient to model the conditions of the original packaging can be used.

Before starting the tests, the medicinal product should be tested for all parameters specified in the draft normative documentation. Tests for parameters that do not change during the storage, as well as tests for parameters whose changes during the storage do not cause deterioration of the medicinal product quality, may be omitted from stability protocols for the medicinal product.

Based on the results obtained, the manufacturer (developer) investigating the medicinal product stability determines its shelf life, indicating the type of packaging, required storage and shipping conditions, and provides this information in the draft normative documentation.

A medicinal product stability study should evaluate compatibility of active substances and excipients simultaneously with their stability.

A stability testing program should be designed to take into account the climatic conditions of the region where these medicinal products are expected to be used.

Table 1 shows the mean temperature and humidity values established for respective climatic zones.

Table 1. Mean temperature and humidity values by climatic zones

Climatic zone	Temperature, ˚C	Relative humidity, %
Zone I — moderate climate	21	45
Zone II — subtropical climate with possible high humidity	25	60
Zone III — hot and dry climate	30	35
Zone IVA — hot and humid climate	30	65
Zone IVB — hot and very humid climate	30	75

Note. Climatic zones are divisions of the Earth's climates into 4 zones based on the predominant annual climatic conditions.

It is recommended to carry out stability studies on medicinal products manufactured from different active substance batches.

If necessary, for some medicinal products in such dosage forms as solutions, suspensions, emulsions, etc., the effect of negative temperatures on their stability may be studied (freeze-thaw cycling).

Long-term stability studies of medicinal products

Long-term studies should be carried out in the primary and secondary packaging recommended for the respective medicinal product at a constant upper (the highest) temperature of the specified storage regimen during the entire claimed shelf life.

In some cases, additional tests may be required at the lowest temperature of the specified storage regime (for example, for soft dosage forms, whose physicochemical state may change at low temperatures).

Samples of medicinal products that are put on stability should be tested for quality parameters specified in the normative documentation during the following periods:

- during the first year of storage — every 3 months;
- during the second and third years of storage — every 6 months;
- following the third year of storage — every 12 months;

Accelerated stability studies

The "accelerated aging" method is mainly used to determine the shelf life of active pharmaceutical ingredients that are substances with a known chemical structure and medicinal products containing these substances as the active ingredient.

This method is not recommended for plant raw materials, herbal medicinal products, homeopathic medicinal products, thermolabile active pharmaceutical ingredients and medicinal products, immunobiologicals, blood products, etc.

The shelf life determined using the "accelerated aging" method should not exceed 3 years for antibiotics produced by a microbiological or semi-synthetic

process and 2 years for their dosage forms. The method is not applicable to increase the previously determined shelf life of a medicinal product over 3 years.

The "accelerated aging" method involves keeping the test drug at temperatures and humidity exceeding those during the storage in the course of its circulation.

This general article provides recommendations for studies of a medicinal product shelf life by the "accelerated aging" method using a modified temperature regimen. Normally, physicochemical processes occurring in medicinal products accelerate at elevated temperatures, which results in untoward changes in their quality over time. Thus, at an elevated temperature, the time interval during which the controlled quality parameters of the medicinal product remain within the acceptable limits (experimental shelf life) is artificially reduced as compared to the shelf life at the storage temperature. This allows to reduce significantly the time needed to determine the shelf life.

Based on the results obtained during the accelerated aging of a medicinal product, the inverse problem may also be solved, i. e. determining the storage temperature that ensures the specified shelf life.

A shelf life (C) at a storage temperature (t_{st}) is related to the experimental shelf life (C_e) at an elevated temperature of experimental storage (t_e) by the following relationship:

$$C = K \cdot C_E,$$

where the correspondence coefficient is $K = A^{\frac{t_э - t_{хр.}}{10}}$.

The temperature coefficient of the chemical reaction rate (A) is assumed to be 2.5.

Notes

1. The above dependence is based on the van't Hoff equation related to a 2 to 4-fold increase in chemical reaction rates with a temperature increase by 10 °C.

2. In some cases, experimentally determined adjusted values of the coefficient A, as well as shelf lives predicted based on stricter relationships, for

example, the Arrhenius equation, can be used.

Table 2 shows the correspondence coefficient values *K* for various values of the difference between the temperatures of experimental and normal storage at *A* = 2.5.

Table 2. Values of the correspondence coefficients (*K*) by the temperature range

#	(t_e-t_{st}), °C	*K*
1	10	2.5
2	15	4.0
3	20	6.3
4	25	9.9
5	30	15.6
6	35	24.7

Note. Key: *K* — correspondence coefficient of; t_e — the temperature of experimental storage; t_{st} — temperature of normal storage.

For accelerated storage experiments on medicinal products, thermostats, thermal cabinets, stability chambers or other devices should be used that allow to automatically maintain the pre-specified temperature of experimental storage t_e with an accuracy of ± 2 °C during the entire experiment.

The highest temperature of experimental storage should ensure that the results necessary for evaluation of the shelf life are obtained within the shortest time possible. However, this temperature should not exceed the limits beyond which the aggregate state of the drug changes or the packaging material deteriorates.

The following experimental storage temperature limits are recommended:

- for individual substances + 60 °C
- for parenteral solutions in glass containers, tablets, capsules + 60 °C
- for parenteral solutions in polymeric package, ointments, liniments + 40 °C
- for suppositories and aerosols + 30 °C

Test samples should not be exposed to light.

The "accelerated aging" method is not recommended for determination of

the shelf life of emulsions.

Determination of the shelf life by the accelerated aging method should be carried out on at least 3 batches of the medicinal product.

The experimental storage temperature (t_e) should exceed the storage temperature (t_{st}) by at least 10 °C.

The quality of the test samples of the medicinal product should be monitored in relation to the parameters specified in the normative documentation, taking into account the general provisions of this general article.

The quality parameters of the medicinal product during accelerated aging are determined at intervals equivalent to 6 months of storage under the storage conditions specified in the draft normative documentation.

The number of samples of the medicinal product intended for experimental storage should be sufficient to carry out the tests specified in the experimental plan.

The start of experimental storage is considered the time point when the medicinal product is put in a thermostatic device, and the end is either the time point when the experimental storage period corresponding to at least two-year shelf life ends or the time point when the drug quality parameters cease to meet the requirements of the normative documentation.

The periods of experimental storage at various temperatures are presented in Table. 3.

Table 3. Periods of experimental storage by the temperature range

#	Shelf life	(t_e-t_{st}), °C	Experimental storage periods, days
1	2 years	10	292
		15	182
		20	116
		25	74
		30	47
		35	30
2	3 years	10	438
		15	274
		20	174
		25	111
		30	71

		35	45
3	4 years*	10	584
		15	365
		20	232
		25	148
		30	94
		35	60
4	5 years*	10	730
		15	457
		20	290
		25	185
		30	117
		35	74

Note

*** –** in case the shelf life is confirmed to be equal to the previously approved one.

Key: t_e – temperature of experimental storage; t_{st} – temperature of normal storage.

In order to calculate the shelf life, the experimental shelf life expressed in days (or hours) is multiplied by the correspondence coefficient *K* (see Table 1).

If the time period C_o between the date of manufacture/production of the medicinal product and the start of its experimental storage exceeds 30 days (but is not more than 90 days), and it was stored during this time under normal conditions, the shelf life *C* is calculated using the following equation: $C=K\cdot C_e+C_o$.

If shelf lives determined on various batches of the medicinal product differ from each other, the minimum of the values obtained is taken as the shelf life.

If necessary, the temperature t_{st} allowing to ensure the specified shelf life *C* is calculated using the following formula:

$$t_{st}=t_e+\frac{10}{\lg A}\cdot \lg\frac{C_e}{C}$$

The data obtained using the accelerated aging method should be supported by the enterprise's (developer's) commitment to continue stability studies under long-term testing conditions throughout the claimed shelf life.

Stability studies by extrapolation method

With sufficient justification, the data obtained in long-term stability studies may be extrapolated.

The extrapolation is performed using statistical data processing. If the results obtained indicate a slight degradation and a slight variation, the statistical analysis

may be omitted.

By extrapolation method, the suggested shelf life can be increased by no more than 2-fold, but maximum for 12 months, as compared to long-term tests.

The data obtained using the extrapolation method should be supported by the enterprise's (developer's) commitment to continue stability studies under long-term testing conditions throughout the claimed shelf life.

Stability studies by bracketing method

When studying the stability of medicinal products, a bracketing study may be carried out.

When using the bracketing method, only samples with extreme variants (limits) of factors (for example, strength, package (container) size and (or) nominal volume) are tested using a full protocol. Such a protocol assumes that the stability of any intermediate variants corresponds to the stability of the extreme variants tested.

Bracketing studies can be used for several strengths with proportional compositions; in case of the same type of package, if, all other things being equal, there are differences in the package size or the nominal volume of the medicinal product.

Matrixing stability studies

When using matrixing, only a subgroup of the total number of samples of all combinations of test factors is tested at a certain time point. Another subgroup of samples of all combinations of factors is tested at the next time point. Various factors of the same medicinal product include, for example, a combination of various batches, various strengths, various sizes of the same container closure system and, in some cases, various container closure systems.

The matrixing method can be used on several strengths with identical or similar compositions.

Studies of the package effect on stability of the medicinal product

Changes in the medicinal product quality may be caused by its interaction with the packaging system, including closures. If the absence of interactions cannot be ruled out for liquid medicinal products (other than those in sealed ampoules), stability tests should include samples in inverted or horizontal positions (i.e., samples that contact the closure, for example, a stopper), along with vertically placed samples, in order to determine the effect of the closure material (stopper) on the medicinal product quality. The results of experimental studies should record all combinations of various container closure systems of tested medicinal products.

For medicines in multi-dose packages, in addition to the standard data required for a conventional disposable package (for example, vial), the applicant must carry out tests that confirm the package ability to withstand reopening/closing while maintaining the medicinal product quality and efficacy throughout the period of its use.

The main factors that affect the medicinal product after opening the package include microbial contamination and physicochemical degradation.

A stability study of medicinal products after opening the primary package should include at least 2 batches, while at least one batch should be expiring.

Parameters should be tested for conformance to the normative documentation requirements at the first time point, at least one intermediate time point, as well as the last time point of the proposed shelf life of the opened medicinal product.

The drug should be tested for all parameters specified in the normative documentation that may change during storage (except for parameters whose changes during storage cannot cause any deterioration of quality), and tests must include microbiological purity or sterility.

Stability studies of medicinal products after reconstitution or dilution

If a reconstituted solid medicinal product or a diluted concentrated medicinal product is expected to be stored for a certain period, stability studies should be carried out on the product prepared in this way.

The objective of stability studies of reconstituted medicinal products is to

determine the period after reconstitution or dilution of the product, during which its quality continues to meet the normative documentation requirements and the product may be used for its intended purpose.

Stability studies should be carried out on reconstituted medicinal products prepared using all possible solvents for dissolving/diluting medicinal products, specified in the instruction for use.

The storage conditions of the reconstituted medicinal product may differ from the storage conditions of the parent drug.

In order to confirm the stability of the reconstituted medicinal product, data obtained for 2 batches, with at least one batch expiring, can be provided.

It is recommended to test the parameters for conformance to the requirements of normative documentation at the first and last time points of the proposed shelf life of the reconstituted medicinal product.

The medicinal product should be tested for all parameters that may change during its storage, and the tests must include sterility or microbiological purity.

Stress stability studies and photostability

In addition to determining the shelf life and selecting the storage conditions, stability studies of original medicinal products and active pharmaceutical ingredients should be carried out with the purpose of determining the most harmful effects of external factors (high or low temperatures, moisture, oxygen and other air components, light, etc.) and conditions of their effect.

Stress stability studies can be carried out on one batch of the medicinal product.

An integral part of stress stability studies is a photostability study.

The scope of medicinal product studies should be determined based on the presence or absence of changes resulting from the exposure to light.

Storage conditions for medicinal products, specified in the normative documentation, must be followed at all stages of the drug circulation.