Guideline for the Stability Testing of Nonprescription (OTC) Drug Products Not Regulated by an NDA/ANDA

Adopted: June 24, 2009

Amended: June 26, 2012; June 3, 2021

Introduction

This guideline is intended to provide the non-prescription drug industry a directly applicable stability testing guideline for OTC monograph drug products not regulated by an NDA/ANDA (hereafter OTC monograph drug products). Historically, non-prescription drug companies developed their stability testing programs based upon their best interpretation and practical application of the most current FDA and/or ICH guidance for new drug products. The FDA has issued a guidance recommending that owners of NDA/ANDAs follow the stability recommendations provided in ICH stability guidance for drug substances and drug products. Because of the unique requirements associated with new OTC monograph drug products, the direct application of the FDA and ICH guidance is sometimes inappropriate and impractical. Drug products with an OTC monograph will typically contain drug substances and excipients that are well characterized with a significant body of information, a ***well-known*** safety profile, and a long history of use in multiple dosage forms. In addition, OTC drug products are exempt from some of the regulatory filing requirements associated with NDA/ANDA products. For these reasons, the OTC industry is offering this guideline for OTC drug products. It follows ICH guidelines to the extent practical and presents data-based, body-of-evidence situations where deviations from ICH guidance may be scientifically justified. Alternative approaches may be used with appropriate scientific justification.

Objectives of the Guideline

This guideline is intended to define the minimum stability data package needed to support the commercial distribution of new OTC monograph drug products in the United States *per climatic zone II*. The stability data package will be based on development stability studies performed by the manufacturer. Stability and material characterization information available from suppliers or peer-reviewed literature may be used to supplement the stability data package. These studies will be used to establish the tentative expiration dating period and label storage statement for the OTC monograph drug product.

Scope of the Guideline

This guideline applies specifically to OTC monograph drug product stability. This guideline does not currently seek to cover the stability testing of:

Non-prescription drug products regulated by an NDA/ANDA

Drug substances

Drug products used in clinical trials

General Principles

The purpose of product stability testing is to provide evidence on and document how the quality of a drug product in its marketed package configurations changes with time under the influence of environmental factors such as temperature, humidity, and light; to establish a shelf-life period; and to recommend storage conditions for the drug product.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions only in the United States.

The design of the stability studies for the OTC monograph drug product should be based on knowledge of the behavior and properties of the drug substance and drug products that use the same active ingredient(s), manufacturing process, quantity of excipients, and container/closure system. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

Knowledge of the Drug Substance

Typically, drug substances used in OTC monograph products are well characterized and their process impurities and degradation products well understood from a chemical and safety perspective. An OTC monograph product manufacturer with extensive experience with the drug substance can build on this to target likely changes to the product's stability at the recommended test conditions. If the drug substance is new to the OTC drug product manufacturer, it is important that both the impurity profile and stability profile of the drug substance be understood prior to initiating a formal drug product stability program. Typically, the manufacturer of the drug substance has process impurity information either on the Certificate of Analysis or available on request. Stability-indicating procedures are expected to separate process impurities from the drug substance and potential degradation products, even if the process impurities are not degradation products.

For many drug substances used in OTC drug products, there is extensive stability data either in the literature or available from the drug substance manufacturer. This information should be obtained or generated prior to the validation of a stability indicating procedure. If the information is not available and needs to be generated by the drug product manufacturer, ICH Q1A Section 2.1.2 provides guidance on potential stress-test protocols.

Interactions between the drug substance and excipients used in the formulation are also important. For OTC drug product manufacturers with extensive experience with an API and a range of excipients used in similar products, stability changes expected from the formulation or changes to it may be straightforward. If using potentially reactive excipients not used in current commercial formulations involving the drug substance, consider potential drug substance-excipient reaction products when developing stability indicating procedures.

Photostability Testing

Stability data should be available to demonstrate if the drug product is susceptible to degradation due to light. At least one batch of the drug product packaged in the container closure proposed for market should be tested for photostability effects. This testing may be omitted if a scientific justification can be provided to show that the drug product in the container closure proposed for market will not be susceptible to photostability effects.

The irradiation of the packaged drug product is to be conducted according to the ICH Q1B guidance for photostability testing of drug products. If not all the listed parameters are appropriate for the product to be tested, document the scientific judgment used to determine the appropriate subset of parameters required for the photostability assessment.

Selection of Batches

For new product formulations where similar marketed-product formulations exist, stability data should be available on at least one (1) primary batch of the drug product. For new product formulations where little or no similar marketed-product formulations exist, additional primary batches may be necessary. Stability data for new non-prescription drug products regulated by an NDA/ANDA should be provided on at least three (3) primary batches as recommended by ICH Q1A. FDA Scale-Up and Postapproval Changes (SUPAC) guidelines can provide guidance and justification for the number of primary batches sufficient for new product formulations where similar formulations exist. The justification for the use of one primary batch should be documented.

The primary batch(es) should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. The primary batch should be at least pilot scale (1/10 Production Scale). For additional primary batches, a scientific rationale should be provided to justify a smaller batch size. Where practical, if multiple batches are studied, the drug product should be manufactured using different batches of the drug substance. Stability studies should be performed on each individual strength, container size, or other attribute unless a reduced sampling and testing program can be scientifically justified (e.g., bracketing and/or matrixing approaches per ICH Q1D can be used).

Container/Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. The use of a surrogate representative package made of the same materials and with equivalent (or worst case) barrier properties is considered acceptable when multiple primary batches are initiated on stability.

Specifications

A specification is composed of a list of tests with references to analytical procedures and their proposed acceptance criteria. The acceptance criteria can be numerical limits or ranges, textual descriptions, or other requirements depending on the type of test specified.

The list of tests should include an assessment for all the drug product attributes that are susceptible to change during storage and that are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes as well as preservative content and effectiveness (e.g., microbial or anti-oxidant) and functionality tests (e.g. for a dose delivery system). Analytical test procedures should be fully validated and stability indicating. There are some test methodologies where it may not be necessary or appropriate, using good scientific judgment, to validate a test procedure (e.g., tablet hardness, where a calibrated test instrument is used, or a compendial procedure, where verification may be sufficient).

Acceptance criteria for shelf-life specifications should be based on all the available stability information and compendial requirements. Specifications for product release may be more restrictive than shelf-life specifications to account for changes observed during storage of stability samples and anticipated during the shelf life of the product.

For multi-dose liquid and semi-solid drug products, antimicrobial preservative effectiveness testing (AET) should be demonstrated in the multi-dose container(s). If differences between the release and shelf-life acceptance criteria for AET are necessary, the difference should be scientifically justified based on a correlation between preservative content and

preservative effectiveness.

Testing Frequency

At the long-term storage condition, the frequency of testing for the primary stability studies should be designed to adequately determine the stability profile for the drug product. This testing frequency will typically be 0, 3, 6, 9, 12, 18, 24 months and annually thereafter through the proposed shelf-life. Justification for doing fewer than these time points should be provided.

At the accelerated storage condition, a minimum of three time points is recommended to be tested over a three-month period (including the initial and final time; e.g., 0, 1, and 3 months). Additional interval(s) through 6 months (e.g., 4.5 and/or 6 months) may be considered. Conducting stability testing through 6 months at accelerated storage condition increases the technical product knowledge on any potential variability of the new formulation stored for an extended period of time.

Storage Conditions

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and its sensitivity to moisture gain or loss, and, if applicable, its sensitivity to potential for solvent loss, oxidation, and light. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Long term and accelerated storage conditions for drug products are detailed in the sections below. The general case applies if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

Container orientation (e.g., on a side, inverted) should be considered when designing stability study protocols for liquid and semi-solid products.

Storage Conditions – General Case

Study	Storage Condition
Long Term	25 ± 2°C / 60 ± 5% RH
Intermediate	30 ± 2°C / 65 ± 5% RH
Accelerated	40 ± 2°C / 75 ± 5% RH

If at the accelerated storage condition the drug product fails to meet the established shelf-life criteria, alternative accelerated conditions (such as and including the intermediate condition) may be used to ensure that at minimum, some acceptable accelerated data is available to show that the product can withstand the typical excursions experienced in the distribution chain once the product is marketed.

Storage Conditions – Drug Products Packaged in Impermeable Containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

Storage Conditions – Drug Products Packaged in Semi-Permeable Containers

Aqueous-based (those containing ≥ 50% water) products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below, on batches/stability studies used to support launch/commercialization. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage Condition
Long Term	25 ± 2°C / 40 ± 5% RH or 30 ± 2°C / 35 ± 5% RH
Intermediate	30 ± 2°C / 65 ± 5% RH
Accelerated	40 ± 2°C / NMT 25% RH

It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH. If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

For long-term studies conducted at 25°C/40%RH, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C if significant change other than water loss occurs during the 3 months testing at the accelerated storage condition. A significant change in the water loss alone at the accelerated condition does not necessitate testing at the intermediate storage condition.

A 5% loss in water from the initial value is recommended to be the limit of acceptability for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40°C/NMT 25% RH. This testing may be performed on 1 batch/study minimum. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing all of the launch/supporting stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated. For example, at a given temperature, e.g., 40°C, the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative Relative Humidity	Reference Relative Humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

Storage Conditions – Special Case

ICH Q1A provides guidance for drug products stored at refrigerated or -20°C conditions. Deviation from these guidelines should be scientifically justified. Drug products intended for storage below -20°C, or under other conditions should be treated on a case-by-case basis.

Post-Launch Stability Requirements

Post-launch marketed product stability testing will be conducted to confirm the assigned expiration dating period as required by the current Good Manufacturing Practices (cGMPs). Data from long-term stability studies for the first three production batches, (specifically if the primary batches were not production scale) and then one batch annually thereafter, for the proposed shelf life of the product provide strong evidence of good long-term stability for commercial product. Reduced requirement may be used if scientifically justified. Requirements for minor or moderate changes to marketed products, such as line extension are typically less stringent and covered in a separate document*.

Evaluation

A scientific approach should be adopted in the presentation and evaluation of stability information for establishing a tentative expiry period. Results from research and development batches on similar or closely related formulations, on similar or closely related marketed products, and data published in the literature or available from suppliers, as well as

results from the specific stability study may be considered a body of knowledge that can be used in the scientific assessment. Results from physical, chemical and microbiological tests as appropriate for the dosage form should be included in this evaluation.

For OTC monograph products new to a manufacturer or with minimal previous history on the market, the purpose of the accelerated stability study is to establish, based on testing a minimum of one batch of the drug product, a tentative expiry period and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances.

When the data from an accelerated stability study remain within established limits, while maintaining potency, a tentative expiry period can be assigned prior to marketing the product. A twenty-four month expiry period may be assigned upon successful completion of three months accelerated testing. For those products that cannot tolerate 40°C accelerated testing, six months' stability data at the intermediate condition (such as 30°C/65%RH) may be used to support a tentative expiry period of twenty-four months. Using sound scientific judgment, shorter expiry periods may be assigned based on less than three months of accelerated testing. Any longer tentative expiry period or extension of an expiration dating period should be made based on scientific justification, historical data on same/similar formulas/products, and calculations using the Arrhenius equation (all with appropriate documentation).

When the data clearly exhibits no change or stability trend over time, a formal statistical analysis is not necessary.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean intersects the acceptance criterion. If analysis shows that the batch-to-batch or among package configuration variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches or package configurations. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance. If it is inappropriate to combine data from several package configurations, then each configuration should be evaluated separately with an expiry period being assigned to the individual package configuration.

Statements/Labeling

A storage statement and an expiration date should be established for the labeling in accordance with current FDA or USP requirements. The statement and expiration date should be based on the demonstrated stability of the drug product. Terms such as "ambient conditions" or "room temperature" should be avoided. Where applicable, specific storage instruction should be provided, e.g., "Protect from excessive heat (temperatures above 40°C (104°F))", "Protect from light", "Protect from freezing".

An expiration date should be displayed on the container label.

Glossary

The following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

Studies designed to increase the rate of chemical or physical change of a drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. However, results from accelerated studies are not always representative of similar results from the long-term label storage studies.

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Container/Closure system

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Development studies

Stability studies initiated during the development of a drug product. If these studies are to be used for the purpose of assigning a tentative expiration dating period, they are sometimes called “formal” stability studies.

Dosage form

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product

The dosage form in the final immediate packaging intended for marketing.

Drug Substance

The unformulated active pharmaceutical ingredient that may subsequently be formulated with excipients to produce the dosage form.

Excipient

Anything other than the drug substance in the dosage form.

Expiration date

The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal stability studies

Stability studies initiated during the development of a drug product in a specific package according to a prescribed stability protocol in order to establish or confirm the shelf life or expiration dating period for the product.

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Line Extension

A product line extension is the use of an established product brand name for a new item in the same product category. Line extensions occur when a company introduces additional items in the same product category under the same brand name such as new flavors, forms, colors, added ingredients, package sizes.

Long term testing

Stability testing of samples that have been stored at the proposed (or approved) labeled storage condition for a drug product in a specific package. Samples are stored and tested through the entire shelf life period.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Pilot scale batch

A batch of a drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Primary batch

A batch of a drug product used in a formal stability study for the purpose of establishing an expiration dating period. A primary batch of a drug product should be at least a pilot scale batch; a scientific rationale may be used to justify the use of a smaller batch.

Production batch

A batch of drug product manufactured at production scale using production equipment in a production facility.

Semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient.

Shelf life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification – Release

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification – Shelf life

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product throughout its shelf life.

Storage condition tolerances

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing (drug substance)

Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product)

Studies undertaken to elucidate the intrinsic stability of the drug product. Such studies include photostability testing and specific testing on certain products (e.g., creams, emulsions).

Supporting data

Data, other than those from formal stability studies that support the analytical procedures, the proposed shelf life, and the label storage statements. Such data include (1) stability data on small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

Tentative Expiry Period

A shelf-life for a drug product in a specific package that has been established using either accelerated or less than full term stability data. A tentative expiry period becomes a shelf-life period once acceptable long term stability data are available to confirm the tentative period.

References

ICH Q1A "Stability Testing of New Drug Substances and Drug Products"

ICH Q1B "Photostability Testing of New Drug Substances and Products"

ICH Q1D "Bracketing & Matrixing Designs for Stability Testing of New Drug Substances and Products"

**CHPA Guideline for the Stability Testing in Support of Changes to Nonprescription (OTC) Monograph Drug Products Not Regulated by an NDA/ANDA*

ITG-41 (FDA) "Expiration Dating and Stability Testing for Human Drug Products"

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