The International Pharmaceutical Excipients Council

Excipient Stability Guide

For Pharmaceutical Excipients

Version 2
2022

This document represents voluntary guidance for the excipient industry and the contents should not be interpreted as regulatory requirements. Alternatives to the approaches in this guide may be used to achieve an equivalent level of assurance for excipient quality.

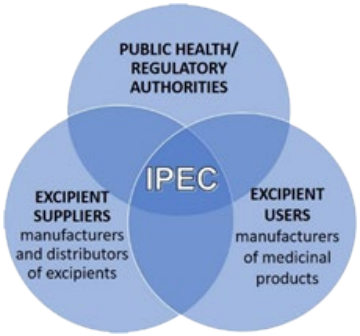
This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and users. At the time of writing there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to international excipient standards development and harmonization, provide information useful for new excipient development and introduction, and offer best practice and guidance concerning excipient development.

IPEC has three major stakeholder groups:

1. Excipient manufacturers and distributors, defined as suppliers in this document,
2. Medicinal (drug) product manufacturers, defined as users in this document, and
3. Public health and regulatory authorities.



This guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the rules and regulations applying to excipients will vary from region to region and country to country. In addition, the rules and regulations are continually evolving. It is the responsibility of the reader to review the latest version of the applicable regulatory guidance; however, the version referenced in the guide will be based on the version available at the time the guide was published.

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In this guide, pharmaceutical excipient(s) will be referred as excipient(s). This guide may be applied to veterinary medicines, as appropriate with reference to specific veterinary guidance and regulations.

Throughout the guide, justification implies that a decision is made based on a scientific, quality and/or regulatory considerations.

This guide offers best practice and guidance in the establishment of an excipient stability program. The excipient supplier may be a manufacturer or a distributor (or both). The guide highlights the factors to consider when planning and executing a scientific study that will determine the stability of an excipient.

*Note: Refer to the "International Pharmaceutical Excipients Council Glossary: General Glossary of Terms and Acronyms [1]" for definitions. The first use of a term found in the glossary will be in **BOLD**.*

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This guide was developed by representatives from International Pharmaceutical Excipients Council (IPEC) member companies. IPEC is an industry association whose members consist of excipient manufacturers, distributors, and users.

IPEC greatly appreciates the many hours devoted by the core team of individuals and other contributors listed below, to make this guide available to IPEC members and the broader excipient community. Equally, IPEC extends thanks to the employers of those same contributors who provide the necessary time and resources, without which, this guide would not be possible.

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1 INTRODUCTION

1.1 Purpose

Since **excipient**s are different from **active pharmaceutical ingredients** (APIs) and **medicinal products** this document provides appropriate guidance for developing supporting studies for excipients, and how this information may be disclosed to **user**s and regulators. The guideline is intended to provide excipient **manufacturer**s with strategies for assessment of overall stability as well as provide an approach for a manufacturer to establish a stability study program which includes study design. Stability studies may be used to support regulatory filings, aid in maintaining the quality of the excipient, and to define and substantiate recommended storage conditions and **shelf-life** claims (e.g., **re-evaluation date**, **expiration date**, and use-by date).

Conformance to this guide also gives confidence to the pharmaceutical end user that an excipient will continue to meet the excipient manufacturer's **specification**s or **monograph** requirements if the excipient is stored in an unopened container at its recommended storage condition up to the shelf-life claim.

1.2 Scope

This guide is applicable to all excipients including those that are new or chemically novel. Information in the guide may also apply to excipients used in veterinary medicines. When implementing this guide, excipient manufacturers should consider how it applies to their specific products. *The term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that provides at least an equivalent level of quality assurance. Note that "should" does not mean "must" or "shall".*

1.3 Principles Adopted

This guide is intended to be of international application. As an international guide, this document does not specify legal requirements nor cover particular characteristics of every excipient. Although this guide acknowledges that the stipulations in International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1A and World Health Organization (WHO) guidelines are not appropriate for excipients because their scope is intended for drug substances and drug products, they can be utilized to provide the principles of, or basis of, an excipient stability program. For example, an excipient manufacturer may not perform stability activities in the same manner or to the same extent as the pharmaceutical industry, however, many activities leading to the same degree of assurance are performed.

This guide includes notes that offer common examples for interpretation and implementation without adding further requirements. Notes are not intended to contain an exhaustive list. They are presented as indented, italicized text.

2 EXCIPIENT STABILITY PROGRAMS

2.1 General Guidelines

The primary purpose of an excipient stability study is to provide evidence that the excipient will continue to meet manufacturer's specifications, define recommended storage conditions in its sealed commercial packaging, determine shelf-life, and establish shelf-life claims. Any stability issues subsequent to opening the package are the responsibility of the user or any party carrying out re-packaging processes.

A suitable program for development of data is described in this document.

2.1.1 Classification of Excipients

The stability of excipients varies. To foster communication between the excipient manufacturers and users, their stability may be described as falling into one of several broad classifications based upon the stability of the excipients in their commercial packaging. These classifications are determined from available stability information from internal and/or external sources. Additional requirements, such as documentation and study requirements, are addressed in subsequent sections below.

Very stable:

- Excipients that have demonstrated a retest/re-evaluation interval or expiration date of 60 months or greater in their specified commercial packaging.
- Stability is not expected to be altered by changes in the manufacturing process.
- Packaging may be a limiting stability factor.

Stable:

- Excipients that have demonstrated a retest/re-evaluation interval or expiration date of at least 24 months but less than 60 months in their specified commercial packaging.
- Generally, more sensitive to changes in the manufacturing process or commercial packaging than excipients classified as Very Stable.

Limited Stability:

- Excipients that have demonstrated a retest/re-evaluation interval or expiration date of less than 24 months in their specified commercial packaging.
- These excipients may be at higher risk from changes to the manufacturing process, raw materials, environmental or product packaging, or other factors that cause it to no longer comply with product specifications.

Note: an excipient can be categorized in more than one classification depending on the protection given to it by the commercial packaging and/or storage conditions. For example, while

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an excipient susceptible to oxidation whose commercial packaging allows exposure to air could be classified as Limited Stability, it may become Very Stable or Stable if packaged under conditions to protect it from exposure to air.

2.1.2 Considerations for New or Chemically Novel Excipients

For excipients where the stability profile has not been established, stability data is needed. For new or **novel** chemical **excipients**, the classification may change during the development program as stability data becomes available.

2.1.3 Considerations for Modifications to Excipients

For modifications to an existing product, changes which may impact product stability should be evaluated, defined, and documented as described in the Significant Change Guide [2]. Risk assessment [3] should be used to determine if the change is significant and stability studies are required.

New packaging shown to be equivalent or better through other studies (e.g., moisture vapor permeation, or oxygen permeation) may not require a new stability study. However, the justification for not conducting a study should be documented. Depending on documented results from a risk analysis, such studies may run concurrently with the change.

2.1.4 Ongoing Stability Studies

Ongoing stability studies should be performed on stable and limited stability excipients with a shelf-life claim.

- **Very Stable Excipients**: It is not necessary to perform ongoing stability studies on products with a shelf-life claim.
- **Stable Excipients**: The frequency of ongoing stability studies should be based upon documented risk assessment and scientific justification.
- **Limited Stability Excipients**: Ongoing stability studies are recommended, and where appropriate, accelerated storage conditions in packaging that properly simulates the packaging container/closure system.

2.1.5 Documentation

Stability information which may include stability data should be available. However, stability data is sometimes proprietary (e.g., compositional details) and under such circumstances sharing the data with users may be handled under confidentiality agreements, to protect the manufacturer's intellectual property. A statement or reference to stability information, in relevant packaging, should be available to demonstrate stability to users. For the classification of excipients, the following should be considered:

- **Very Stable Excipients:** A summary report which includes pertinent data (e.g., stability indicating characteristics, literature citations, trending analytical results, monitored/recorded storage conditions) should be available to the user upon request.
- **Stable and Limited Stability Excipients**: A summary report supported by ongoing studies which includes pertinent data (e.g., stability indicating characteristics, stability study data, literature citations, storage condition monitoring) should be available to the user upon request.

Where there is insufficient data to support classification of an excipient, data should be obtained from a stability study (see Section 2.2).

2.2 Stability Studies

Three options for design of an excipient stability study are listed below. Options 1 or 2 are expected to apply in most situations.

1. Utilize historical data including that found in the literature and generate a report summarizing the data and drawing conclusions about excipient stability.
2. Conduct a study using the excipient packed in the commercial packaging placed in one or more warehouses which are used to hold commercial stocks.
3. Conduct a study using controlled conditions and/or recommendations from ICH Q1A(R2) [4] and/or WHO [5].

Option 1 examples of suitable historical data could include:

- An excipient stored in a warehouse for a defined period, retested at the end of the storage period, and the results confirmed that the product was still within specifications.
- Documented evidence that product still has the desired **functionality** as an excipient after a defined period of time.
- Published data, public and/or internal to the company (e.g., journal articles, etc.) can be cited.

In Option 2 generating data using the actual commercial packaging and storage conditions is ideal, especially as those conditions are often uncontrolled (i.e., with regard to humidity and temperature). Suitable historical data can include retest/re-evaluation results on batches that have been held by the manufacturer for a long period of time, or other equivalent data on actual batches held in the supply chain.

Option 3 may be used for novel and new excipients where stability data in accordance with Options 1 or 2 are unavailable. As noted in the IPEC-PQG GMP Guide [6] for excipients available in multiple grades, bracketing and matrixing studies, as described in ICH Q1D [7], may also be appropriate. There should be evidence of the time intervals between the testing and there should be evidence of the storage conditions used. The commercial packaging should be defined and

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the general conditions under which the samples or containers are stored should be known. A warehouse monitoring and/or mapping study in conjunction with facility maintenance records could be used to support this historical data, especially if the excipient can be shown to be stable under a wide range of storage conditions.

The aim of the stability study should be to provide evidence that the excipient is stable under the likely storage conditions. Excipients can be stored under uncontrolled warehouse conditions, unless specified storage conditions are required to ensure excipient stability. A warehouse monitoring program should be established if these conditions are not known. The temperature in the area of the warehouse where the study was conducted and commercial product will be stored should be monitored over a period of at least one year (to understand maximum and minimum temperature ranges due to seasonal variations), and ideally for the duration of the study. Humidity should also be monitored, especially if the excipient is hygroscopic or otherwise adversely affected by moisture and the packaging is known to be permeable to moisture.

Uncontrolled warehousing conditions vary with geographical locations. If the excipient is shipped to regions which have environmental conditions well outside the parameters evaluated in the stability study, then additional studies may be needed to show stability at a region's conditions. This may be defined by using a tool such as mean kinetic temperature (MKT).

2.3 Stability Protocols

Stability studies should be described in a protocol with details including:

- Objective of the study.
- Scope of the study including justification for materials chosen and number of batches to be tested (at least 3 should be selected in the first instance where stability data, including in the literature, does not exist).
- Selection and justification for the **grade** selected where model studies or multiple grades are produced (could include risk assessment/justification for how to include samples produced at multiple sites, using same starting materials, same formulation, equivalent equipment/processing, and packaging).
- Selection and justification of batches (e.g., typical of production).
- Selection and justification of packaging, accounting for the worst case when multiple packaging types are used.
- Storage conditions.
- Sampling plan.
- Stability test methods.
- Acceptance criteria.

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2.3.1 Objective

The purpose in conducting the stability study should be clearly stated. It is important to note whether the study is being conducted to support a new excipient, to evaluate the impact of a change, or is part of an ongoing stability confirmation.

2.3.2 Scope

The protocol should clearly indicate which excipient or grades of excipient are covered by the stability study, especially where the protocol is applied to a “model product” study [6] or a matrix design is used [7].

Samples from lots selected to represent as broad a range as feasible, within the normal variation of the product related to the stability indicating parameters, should be placed on stability. Ideally at least three different batches of product should be subject to the initial stability study, but a single batch may be initially appropriate until more batches are available. A single **batch** is typically appropriate for ongoing stability program studies.

For new excipients, developmental lots can be used to provide information on the stability of the excipient. However, it is recommended that three or more commercial scale lots are used to confirm the stability of the excipient.

2.3.3 Selection and justification of representative batches

The selected batches should cover the normal production range (including filling/packaging), considering, where possible, worst case in terms of specification parameters, particularly the stability-indicating parameters.

Batches should be manufactured with different batches of critical raw materials, when possible. If not feasible, written justification should be documented as part of the protocol.

2.3.4 Selection of packaging for stability studies

In selecting the packaging for conducting the stability study, the same care and consideration should be given to both the container and closure system [8]. In particular the package sealing/closure system should ideally be the same as the commercial packaging.

Alternative packaging that provides significantly less protection can lead to a shorter retest/re-evaluation interval than would be provided by the commercial packaging. However, using packaging providing less barrier protection is often used to simulate a 'worst case' for protection of the excipient in normal commerce, provided it is backed by sound scientific justification and demonstration that the excipient composition profile does not change.

For example, the least protective packaging for solid excipients is typically an unlined paper bag or a single ply plastic bag. When selecting a container that is an alternative package to use for the stability study, the package with greater surface area/kg of product, such as a small container

rather than a large container should be selected. Another consideration for an alternative container is one with materials of construction or closure systems known to be more permeable than the commercial packaging system.

Stability studies for bulk shipments (e.g., barges, railcars, tank cars, etc) pose particular problems in the design of an appropriate stability study as there is some uncertainty as to how long the excipient may reside in the bulk container. However, extrapolation from data collected using the methods outlined above (see Section 2.2) may be possible where consideration is given to the risk factors for excipient stability that are posed by these modes of transport and storage.

2.3.5 Storage Conditions

Stability samples should be stored under the specified storage [9, 10, 11] conditions as defined in the protocol, or the conditions found in the manufacturer's warehouse when appropriate. The stability study should be conducted over the longest period that the excipient supplier warrants the product will continue to conform to the specification in the commercial package using the recommended normal warehousing or specified storage conditions. Extrapolation of data from these stability studies to justify a warranty more than the duration of the stability study should be justified.

If the manufacturer suspects, based on literature or data, that the excipient degrades under normal warehouse conditions, the study should be performed using specified conditions that challenge the stability of the excipient. For example, if it is known that exposure to atmospheric moisture hydrolyses the excipient, the storage conditions for the stability study should be similar to the specified storage conditions such as "store below 50% relative humidity". In this case, controlled storage and stability conditions and a container/closure system that mimics the commercial package are recommended.

2.3.6 Sampling Plan

The study is best conducted as a kinetics experiment, and thus samples are taken at less frequent intervals as the excipient approaches its expiration retest/re-evaluation interval, for example samples may be tested at 0, 3, 6, 9, 12, 24 and 36 months.

The protocol should specify the frequency, from the **date of manufacture** [12] (time zero), at which samples are to be taken from the stability package for testing. The purpose of the stability study is to confirm that the rate of change in composition if any, is slow enough to allow the excipient to remain within specification for its stated expiration date or retest/re-evaluation interval.

Removal of aliquots of excipient being stored for stability evaluation should be performed in a manner such that the remaining excipient is unaffected. Special consideration is required particularly where the excipient is affected by exposure to the atmosphere, since opening the commercial packaging for sampling exposes the bulk excipient. During and post sampling, the aliquot should also be appropriately protected from the atmosphere.

Where exposure during sampling can affect the excipient, consideration should be given to individual packaging that simulates the bulk package. This facilitates the retrieval of samples for testing without affecting the remaining excipient being stored for future stability testing.

2.3.7 Stability Test Methods

In the pharmaceutical industry, stability testing of the dosage form often relies on the assay as the stability indicating test method. However, this is often neither possible with excipients nor the preferred way to monitor excipient stability. When the excipient is known to change during the stated retest/re-evaluation interval, it should be tested using an appropriate validated/verified, stability indicating test(s) that demonstrate changes to the product. Ideally such changes should be determined using a method that yields a quantitative result.

The stability of excipients can be monitored using a stability indicating assay method. However, where there is no direct measurement of the purity of the excipient, stability may be quantified through the appropriate measurement of other characteristics (e.g., microbiological, physical, or chemical).

Caution should be exercised when monitoring the stability of an excipient using volatile decomposition products. It can be difficult not to lose measurable amounts of decomposition products, and thus not properly monitor excipient stability.

Conformance of the excipient to specification or assay determination may not be the only testing necessary to confirm the stability of the excipient. Consideration should also be given to a comparison of the **composition profile** [13] of the excipient at the limit of its expiration date or retest/re-evaluation interval, as appropriate, to that of the excipient at time zero. The composition profile of the excipient should remain essentially unchanged, unless justified, within the recommended storage conditions.

2.3.8 Out of Specification Results

During a formal study, unexpected results may occur that are Out of Specification (OOS) or Out of Trend (OOT) [14]. These instances should be treated following a formal OOS procedure [5]. Therefore, the design of the stability study should allow for more samples than the study requires in the event of an OOS or OOT result or the loss of a sample.

The key principle is that an OOS or OOT result is not discounted unless there is a clear scientific rationale. Ideally the criteria to dismiss such a result should be pre-defined before the study commences. It is recognized that it may not be clear that a result was out of trend until sometime later in the study and thus an investigation may not be promptly initiated.

2.3.9 Acceptance Criteria

The protocol should establish the limits for test results that are required to support the stated expiration or retest/re-evaluation interval. For each test parameter, an acceptance range or limit

should be specified. Trend analysis of the data should be used as an indication that the excipient will continue to meet specification through its expiration or retest/re-evaluation interval.

When defining the acceptance criteria in the protocol it may include testing beyond the product specification (e.g., composition profile [13]).

Where a stability study identifies degradation products, considerations should be given to degradation product safety [15] and including degradation product specification(s).

2.3.10 Approval Process

The protocol should specify the approval process including an internal review of the data and conclusions. In particular, the protocol should state where the approval responsibility lies, including responsibility for quality oversight.

2.4 Stability Reports

During the course of the program, the excipient supplier may issue interim reports. After all the data has been collected and evaluated against the acceptance criteria, a final report should be prepared. The report should contain a statistical evaluation of the stability data and the conclusions reached, and it should list and justify any deviation from the stability protocol. Statistical tools may be utilized for the determination of retest periods.

The report should include:

- Report type (interim or final).
- Excipient grade(s).
- Commercial packaging, see Section 2.3.4.
- Recommended storage conditions.
- Test results including stability-indicating characteristics and their acceptance criteria.
- Deviations (if applicable).
- Investigations (if applicable).
- Conclusion, including determination of the shelf-life claim and retest/re-evaluation interval, if applicable.
- Document approval.

In addition to the stability report, a summary report may be prepared for excipient users or to support regulatory submissions. Summary reports may be the subject of a Confidential Disclosure Agreement.

2.5 Labelling

Where excipients require specific storage conditions, to preserve their quality during their shelf-life claim in the commercial packaging, the storage conditions required should be stated on the **label** and/or other literature (e.g., Certificate of Analysis). Storage conditions are not necessary

on product labels when specific storage conditions are not required. Documentation should be available from the manufacturer to scientifically justify that these conditions are effective in assuring the conformance of the excipient to the excipient manufacturer's specification up to and including the shelf-life claim, in the unopened commercial packaging.

Note: Based upon industrial Enterprise Resource Planning (ERP) systems used, the product safety data sheet may not reflect the exact storage conditions from excipient stability studies.

Where the stability study indicates conditions to avoid, these conditions should be specified on the label. Any specific protection requirements should also be stated on the label (e.g., 'Protect from light'). Labeled storage statements for monographed excipients should align with pharmacopeial requirements (e.g., USP <659> [16], ChP <0251> [17], Ph. Eur. 1. General Notices [18]).

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3 REFERENCES

IPEC documents referenced below can be accessed at the following website links:
IPEC-Americas page: https://ipecamericas.org/
IPEC Europe page: https://www.ipec-europe.org/guidelines.html

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15. IPEC *Safety Guide for Pharmaceutical Excipients*

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