



The International Pharmaceutical Excipients Council

Excipient Stability Guide

For Pharmaceutical Excipients

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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.

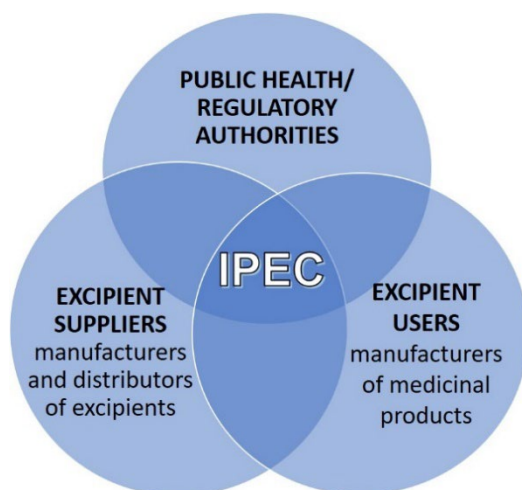
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FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and excipient users. At the current writing there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the 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 *excipient suppliers* in this document
2. Medicinal product manufacturers, defined as *excipient users* in this document
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 laws 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 most current version of any applicable regulatory requirement. Versions referenced in the guide were based on versions available at the time the guide was published.

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

Throughout the guide, justification implies that a decision is made based on 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 Excipient Council General Glossary of Terms and Acronyms” for definitions [1]. The first use of a term found in the glossary will be **BOLD**.*

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1 INTRODUCTION

1.1 Purpose

Excipients are different from **Active Pharmaceutical Ingredients** (APIs) and **medicinal products** and fall outside the scope of the ICH Q1 [2] stability **guidelines**. This guideline is intended to provide excipient **manufacturers** 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. Pre-existing data or formal stability studies may be used to support regulatory filings (e.g., Drug **Master File** (DMF), **Certificate of Suitability to the European Pharmacopoeia** (CEP) filing, other regional regulatory dossiers) 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 medicinal product end **user** that an excipient will continue to meet the excipient manufacturer's **specifications** 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.

1.3 Principles Adopted

This is an international guide. As such it cannot specify all national legal requirements nor cover in detail the particular characteristics of every excipient.

When considering the use of this guide, manufacturers and **distributors** should consider how it may apply to that specific organization's product. The diversity of excipients means that some principles of the guide may not be applicable to certain products and processes. The term "should" indicate 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".

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1 and World Health Organization (WHO) [3] guidelines are applicable to drug substances and medicinal products. They are not directly applicable to excipients. However, the IPEC Stability guide utilized principles in these guidelines to develop excipient stability guidelines and protocols in this Guide. Excipient manufacturers may not perform stability activities in the same manner or to the same extent as drug substances or finished **drug**

products, however, many activities leading to the same degree of assurance are performed. As an example, as compared to drug substances and medicinal products, many excipients are polymeric or naturally derived and may have re-evaluation intervals rather than **expiry dates** and fewer attributes that are stability indicating. Many excipients also do not require tightly controlled storage conditions. The term “shelf-life” is used in this guide to define either the re-evaluation period or the expiry period, depending on the context of use.

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 blue* 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 under recommended storage conditions (where appropriate) in its sealed commercial packaging. Stability studies can also be used to establish the shelf-life claims and the recommended storage conditions. Any stability issues subsequent to opening the package are the responsibility of the user or any party carrying out re-packaging processes.

NOTE: If the original package is opened and the excipient re-packaged, the shelf-life for the repackaged excipient may need to be evaluated.

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**).

A suitable program for development of data regarding the packaged excipient and storage in the unopened package is described in this document.

2.1.1 Classification of Excipients

To foster communication between the excipient manufacturers and users, excipient stability may be described as falling into one of several broad classifications based upon the stability of the excipient 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 re-evaluation interval or expiration date of 60 months or greater in its specified commercial packaging.
- Have stability indicating characteristics (e.g., assay, marker impurities, etc.).

- Stability is not expected to be altered by changes in the manufacturing process.

Stable:

- Excipients that have demonstrated a re-evaluation interval or expiration date of at least 24 months but less than 60 months in its specified commercial packaging
- Have stability indicating characteristics (e.g., assay, marker impurities, etc.).
- Stability may be more sensitive to changes in the manufacturing process, or changes in the packaging, than excipients classified as Very Stable.

Generally, such excipients have been demonstrated to be stable through literature citations and/or stability studies, but their stability is more sensitive to changes in the manufacturing process or product packaging than for excipients classified as Very Stable (e.g., inorganic ionic salts).

Limited Stability:

- Excipients that have demonstrated a re-evaluation interval or expiration date of less than 24 months in its specified commercial packaging.
- Have stability indicating characteristics (e.g., assay, marker impurities, etc.),
- These excipients may be at higher risk from changes in the manufacturing process, **raw materials**, environmental or product packaging, or other factors.

Excipients in this class may be subject to hydrolysis, moisture absorption, thermal or light degradation, viscosity change, oxidation or are otherwise adversely affected by environmental conditions in a manner such that they no longer conform to specification.

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 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.

Where these excipients are hygroscopic, loss on drying or moisture determination can be used as stability indicating tests. Excipients known or suspected to oxidize in air or react with carbon dioxide should be tested using a suitable method that will measure their reaction products. This classification also includes certain organic excipients which have a propensity to develop peroxides.

For these excipients, an on-going stability program is recommended, comprising both long term and, where appropriate, accelerated storage conditions in packaging that properly simulates the packaging container/closure system.

In all cases, the assigned re-evaluation interval or expiration date should be justified based upon sound data and scientific principles, and documented. A summary report, providing information

on stability indicating characteristics, packaging, storage conditions and results of the stability study should be provided to the user upon request.

2.1.2 Considerations for New or Chemically Novel Excipients

For excipients that are new chemical entities where the stability profile has not been established, stability data is needed. The classification may change during the development program as stability data becomes available. When the **novel excipient** is intended for specific applications, such as biologics, the drug product manufacturer should assess the potential interaction between the novel excipient and the drug substance and any impact on the drug product stability as these interactions cannot be evaluated by the excipient manufacturer.

2.1.3 Considerations for Changes to Excipients

Changes should be evaluated, defined, and documented as described in the **Significant Change** Guide [4]. Risk assessment [5] should be used to determine if the change could have an impact on the stability profile of the packaged excipient.

A tiered approach based upon the excipient's stability classification should be applied to define the activities needed to determine the impact of the change on the packaged excipient shelf life (e.g., new stability data is more likely to be needed for significant changes to excipients with limited stability as compared to very stable excipients). The **justification** for conducting new studies, generating new data, or not conducting a study should be documented. Depending on documented results from a risk analysis, studies or generation of new data may not be required.

Stability studies may be necessary to qualify significant changes including, but not limited to, the following:

- Changes in the excipient packaging, including **packaging materials** and packaging process/equipment;
- Changes in the composition of the excipient, including changes to the raw materials and manufacturing process which could have an impact on the excipient composition; and
- Changes in the conditions to which the excipient is exposed during packaging, storage, and transport.
- Changes to packaging materials may be supported by technical documents or studies, if needed, demonstrating equivalent or better protection (e.g., moisture vapor permeation, or oxygen permeation).

2.1.4 Ongoing Stability Studies

Ongoing stability studies frequency should be performed based on the susceptibility for excipient stability to change (refer to option for design of stability studies in section 2.2).

- **Very Stable Excipients:** It is not necessary to perform ongoing stability studies on products.
- **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 in packaging that properly simulates the packaging container/closure system, unless justified and documented.

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 summary report or statement relating to relevant packaged excipient, supported by stability studies (refer to section 2.2, options 1-3) which include pertinent data (e.g., stability indicating characteristics, literature citations, trending analytical results, stability study data, monitored/recorded storage conditions) should be available to the user upon request.

2.2 Stability Studies

The purpose of the stability study is to confirm that the excipient remains within specification for its stated expiry date or re-evaluation interval. Three options for establishing excipient stability 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 to justify and document excipient stability (refer to section 3.1 Using Historical Data in lieu of Formal Studies).
2. Conduct a study using the excipient packed in the commercial packaging placed under inventory conditions which, for example, may be used to hold commercial stocks (refer to section 3.2 Warehouse Studies and 4 Shipping Studies).
3. Conduct a stability study (refer to section 3.3 Using Formal Controlled Stability Studies).

Option 3 is normally necessary for novel and new excipients where stability data in accordance with options 1 or 2 are unavailable. The practice of running stability studies under carefully controlled conditions is only relevant to excipients that require specified storage conditions, or if accelerated testing conditions are used, e.g. for new chemical excipients.

For all options used for studying stability, the aim should be to provide evidence that the excipient is stable under the likely storage and shipping conditions. Excipients can be stored and shipped under prevailing conditions, unless specified storage conditions are required to ensure excipient stability. A monitoring program should be established if specified storage conditions are required.

Prevailing warehousing conditions vary with geographical locations. If an 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 under those conditions. This may be defined by using a tool such as mean kinetic temperature (MKT) or another suitable tool.

2.3 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: Material Safety Data Sheets provided for Health, Safety and Environmental reasons often contain a section about recommended storage conditions. These are only a general indication of the conditions required to assure the safety of the excipient.

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> [6], ChP <0251> [7], Ph. Eur. 1. General Notices [8]) JP General Notice 48)

3 EXCIPIENT STABILITY OPTIONS

As described above in Section 2.2, there are three options for establishing excipient stability. 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 to justify and document excipient stability (refer to section 3.1 Historical Data in lieu of Formal Studies).
2. Conduct a study using the excipient packed in the commercial packaging placed under inventory conditions which, for example, may be used to hold commercial stocks (refer to section 3.2 Warehouse Studies).
3. Conduct a stability study (refer to section 3.3 Formal Stability Studies).

3.1 Historical Data in lieu of Formal Studies

Where an excipient (or bracketed product family of excipients, refer to Section 3.4 Bracketing and Matrixing for more details) has historical data demonstrating that the excipient is inherently very stable, independent of the commercial packaging, then stability studies may not necessary for establishing excipient stability or for marketing that excipient in different packaging formats.

Where very stable excipient (or bracketed product family of excipients, refer to Section 3.4 Bracketing and Matrixing for more details) is dependent on commercial packaging to protect the excipient from environmental impacts that may influence product stability, then historical stability data for the excipient in the package should be used in a risk assessment supporting excipient stability and for marketing excipients in different packaging formats

Justification for using historical data in lieu of formal studies should be documented. Additionally, when formal stability studies in the commercial packaging are not possible (e.g., bulk storage/transport options such as silos, railcars, or tanks) the data used to determine stability should be justified.

Suitable historical data could include:

- An excipient stored in a warehouse for a defined period, re-evaluated 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 attributes 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.

After all the data has been collected and evaluated, a final report should be prepared. The report should contain the justification for the data use and references. In addition to the stability report, a summary report may be prepared for excipient users or to support regulatory submissions. When internal company data is used, summary reports may be the subject of a Confidential Disclosure Agreement.

3.2 Warehouse Studies

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 prevailing warehouse conditions, unless specified storage conditions are required to ensure excipient stability.

Generating data using the actual commercial packaging and storage conditions is ideal, especially as those conditions are often prevailing (i.e., with regard to humidity and temperature). In such cases, temperature and humidity program may be used to justify prevailing warehouse conditions. For warehouses not temperature and humidity monitored or controlled, local weather monitoring sources can be used, Suitable data can include 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**.

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

- Objective of the study
- Scope of the study including justification for using existing product from inventory storage, materials chosen and number of batches tested
- Storage conditions
- Sampling plan
- Stability test methods
- **Acceptance criteria**
- Documented approval

3.2.1 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.

3.2.2 Scope

The protocol should clearly indicate which excipients are covered by the stability study, especially where the protocol is applied to a bracketed product families study or a matrix design [refer to Section 3.4].

3.2.3 Selection of 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 (ingredients that might impact the stability), when possible. If not feasible, written justification should be documented as part of the protocol.

3.2.4 Storage Conditions

The temperature in the area that the samples are stored should be known for the purpose of conducting stability. Humidity should also be known, especially if the excipient is hygroscopic or otherwise adversely affected by moisture and the packaging is known to be permeable to moisture.

For warehouses not temperature and humidity monitored or controlled, local weather monitoring sources can be used.

3.2.5 Sampling Protocol

The predetermined tests established in the stability protocol are to be performed at predetermined test intervals. At minimum, the study should include three test intervals including T_0 (e.g., Lot release or CoA results) and an interval equal to the target shelf-life claim (e.g., 0, 12, and 24 months for a 24-month aging study).

The study is best conducted as a kinetics experiment, and thus samples are taken at less frequent intervals as the excipient approaches its re-evaluation interval.

Samples selected for stability testing should be representative of the manufacturing process and packaged in the same or equivalent packaging (i.e., same materials of construction and similar closure) as intended for market. For bulk excipients, stability samples may be stored in smaller, representative containers.

When collecting samples for stability testing, consideration should be given to excipient exposure to the environment during the sampling process. During and post sampling, the aliquot should also be appropriately protected from the environment. The design of the stability protocol should allow for more samples than the study requires in the event of an OOS result or the loss of a sample.

The protocol should describe the sampling procedure and take into account that portions of the stability sample may not be uniformly affected by environmental conditions. A minimum of three test intervals including the initial and final test intervals are expected. If necessary to extend the study beyond the time frame for which the protocol was initially written, the final time point may be extended by adding an additional test interval.

3.2.6 Stability Test Method

In the medicinal product 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 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).

3.2.7 Out of Specification Results

Results may occur that are Out of Specification (OOS). These instances should be treated following a formal OOS procedure [9].

The key principle is that an OOS 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.

All test results which do not meet acceptance criteria must be investigated per the procedure outlined in firms' OOS investigation policy. Stability study failures must be documented via non-conformance and corrective action systems. The final investigation results and their associated root causes should be documented in the stability study report.

3.2.8 Acceptance Criteria

The protocol should establish the limits for test results that are required to support the stated expiration or 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 re-evaluation interval.

When defining the acceptance criteria in the protocol it may include testing beyond the product specification (e.g., **composition profile** [10]).

3.2.9 Stability 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 **re-evaluation periods**.

The report should include:

- Report type (interim or final)
- Excipient **grade(s)**
- Commercial packaging
- 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 re-evaluation interval, if applicable
- Document approval by quality unit

Extrapolation of data from these stability studies to justify a shelf life more than the duration of the stability study should be justified.

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.

3.3 Formal Stability Studies

Formal Stability Studies are needed when there is no data to support excipient stability such as with new chemical entities. 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 the general conditions under which the samples or containers are stored should be known.

The aim of the stability study should be to provide evidence that the excipient is stable under the likely storage conditions.

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 method
- Acceptance criteria
- Documented approval by quality unit

3.3.1 Objective

The aim of the stability study should be to provide evidence that the excipient continues to meet specifications for a specific period of time under the defined storage conditions. 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.

3.3.2 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 or a matrix design is used [refer to Section 3.4].

Samples from batches 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 batches can be used to provide information on the stability of the excipient. However, it is recommended that three or more commercial scale batches are used to confirm the stability of the excipient.

Accelerated or intermediate conditions can be used if the study is being conducted to support a new excipient or to evaluate the impact of a change for an existing excipient. The protocol should clearly define the accelerated aging conditions.

3.3.3 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 (ingredients that might impact the stability), when possible. If not feasible, written justification should be documented as part of the protocol.

3.3.4 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. 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 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 (refer to 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.

3.3.5 Accelerated Stability Studies

Accelerated aging studies may be used to predict/support a long-term stability study [11]. When accelerated stability studies are run, they should be carried out under controlled storage conditions.

Accelerated stability studies may be used as a risk-based approach to going to market ahead of having full real-time data to support a re-evaluation date or expiration date. These studies are intended to increase the rate of chemical degradation or physical change and to identify possible degradation pathways by using exaggerated storage conditions as part of stability studies. Results from accelerated testing studies are not always predictive of physical changes.

If an accelerated aging study is selected, the accelerated study must be conducted on at least one batch of product.

For accelerated data to be utilized to establish a shelf-life claim, a parallel real time study must be in progress to verify accelerated study assumptions (i.e., the same batch of product must be used in both studies).

3.3.6 Storage Conditions

Stability samples should be stored under the specified storage [12, 13, 14] conditions as defined in the protocol. A long-term 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.

A new stability study should be conducted if a change occurs that may affect the excipient stability (for example in the process or with the packaging or container closure system).

NOTE: Batches of excipient may be subjected to reevaluation if they have been stored within the defined conditions in the unopened package beyond the re-evaluation date, and if the batch is within the expiry interval.

3.3.7 Sampling Protocol

The predetermined tests established in the stability protocol are to be performed at predetermined test intervals, for example samples may be tested at 0, 3, 6, 9, 12, 24 and 36 months. The protocol should specify the frequency from the inception date of the study (T_0) at which samples are to be taken from the stability package for testing.

The study is best conducted as a kinetics experiment, and thus samples are taken at less frequent intervals as the excipient approaches its expiration re-evaluation interval

Samples selected for stability testing should be representative of the manufacturing process and packaged in the same or equivalent packaging (i.e., same materials of construction and similar closure) as intended for market. For bulk excipients, stability samples may be stored in smaller, representative containers.

When collecting samples for stability testing, consideration should be given to excipient exposure to the environment during the sampling process. During and post sampling, the aliquot should also be appropriately protected from the environment. The design of the stability protocol 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 protocol should describe the sampling procedure and consider that portions of the stability sample may not be uniformly affected by environmental conditions.

3.3.8 Stability Test Methods

In the medicinal product 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 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** [10] of the excipient at the limit of its expiration date or 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.

3.3.9 Out of Specification Results

Results may occur that are Out of Specification (OOS). These instances should be treated following a formal OOS procedure [9].

The key principle is that an OOS 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.

All test results which do not meet acceptance criteria must be investigated per the procedure outlined in firms' OOS investigation policy. Stability study failures must be documented via non-conformance and corrective action systems. The final investigation results and their associated root causes should be documented in the stability study report.

3.3.10 Acceptance Criteria

The protocol should establish the limits for test results that are required to support the stated expiration or 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 re-evaluation interval.

When defining the acceptance criteria in the protocol it may include testing beyond the product specification (e.g., composition profile [10]).

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

The methodology to be used for evaluation of stability data to determine the excipient stability should be selected and defined. When there is no relevant or significant degradation, or product

purity is not significantly influenced during storage, a simple comparison of stability data against product specification limits / acceptance criteria may be sufficient.

3.3.11 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 re-evaluation periods.

The report should include:

- Report type (interim or final)
- Excipient grade(s)
- Commercial packaging
- 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 re-evaluation interval, if applicable
- Document approval
- The reevaluation interval for the excipient and where data indicates it, the expiry interval.

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.

3.4 Bracketing and Matrixing

Bracketing involves testing samples at the extreme ends of certain design factors. This assumes that the stability of the extreme samples represents the stability of any **intermediate** levels. The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the factors selected for testing are indeed the extremes. Bracketing can reduce the number of samples included in the stability program by focusing on representative products instead of testing all product offerings.

Additionally, products that share the same stability profiles and design factors such as raw materials, packaging components, etc., may be combined into (bracketed) product families. Product families may be used to reduce stability schedules as the design of product families is such that only select product(s) of the product family will be placed on stability, representing the stability profiles of all other products within the family. The product family design assumes that

the product(s) selected is representative of the family, and therefore the shelf life and shelf-life claim of the product(s) is applicable to the entire product family.

Rationale for the product/grade/packaging brackets should be justified and documented.

3.4.1 Excipient Product Family Factors

Properties of the excipient that change over time are considered stability indicating attributes. These attributes include physical properties, chemical properties, biological properties, and microbiological properties.

Examples of common attributes include, but are not limited to, moisture content and viscosity.

Excipients can be arranged into groups based on similarities in the above properties. The product groupings should list which excipient products/types are included and the list of products should be justified.

3.4.2 Container Closure Sizes and/or Fills

Bracketing can be applied to studies of the same container closure system where either container size or fill varies while the other remains constant. However, if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes by comparing the various characteristics of the container that may affect product stability.

Bracketing should not be applied to container systems with different construction materials unless otherwise justified. (e.g., glass bottles with high-density polyethylene HDPE pails and liners).

Bracketing should be justified if applied to containers made of both different construction materials and of different sizes (e.g., glass bottles vs HDPE pails).

3.4.3 Design Considerations and Potential Risks

Stability studies should be performed on the stated storage conditions. If, after starting the studies, one of the extremes is no longer expected to be marketed, the study design can be maintained to support the bracketed intermediates. A commitment should be provided to carry out stability studies on the marketed extremes.

Before a bracketing design is applied, its effect on the re-evaluation period or shelf-life estimation should be assessed. If the stability of the extremes is shown to be different, the product should be considered no more stable than the least stable extreme (i.e., the shelf life for the intermediates should not exceed that for the least stable extreme). Groupings of products and/or packaging can be utilized to minimize the impact of extremes with different stability.

3.4.4 Design Examples

Table 1 is an example of a bracketing design is based on the use of only two batches for liquid-based excipient. Table 2 captures the use of three batches for a dry excipient material. These examples are provided as conceptual and are not intended for direct use. Alternatives to the approaches may be used to achieve an equivalent level of assurance for excipient stability.

Table 1: Bracketing for Liquid-based Excipients

Concentration		Low		Medium		High	
Batch		1	2	1	2	1	2
Container size	1kg	T	T			T	T
	5 kg						
	12 kg						
	20 kg						
	30 Kg	T	T			T	T

Key: T = Sample tested

Table 2: Bracketing for dry/ powder-based excipients

Particle Size granulated materials		Very Fine			Moderately fine			Coarse		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 kg	T	T	T				T	T	T
	20kg									
	35kg									
	50 kg									
	100 kg	T	T	T				T	T	T

Key: T = Sample tested

4 SHIPPING STUDIES

Shipping (stability) studies can be used to evaluate the effect of short-term temperature exposure during shipping, handling and storage. They may be performed for information purposes only. Shipping studies should consist of scientifically sound and justifiable approaches to evaluating the effect of short-term temperature exposure during shipping, handling and storage. Data from accelerated stability studies can be used to evaluate the effect of short-term excursions outside the defined storage conditions such as might occur during shipment.

5 REFERENCES

IPEC guides 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>

1. The International Pharmaceutical Excipient Council: General Glossary of Terms and Acronyms.
2. ICH Harmonised Tripartite Guideline, ICH Q1A(R2), Stability Testing of New Drug Substances and Products
<https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf>
3. Annex 10, WHO Technical Report Series 1010, Stability testing of active pharmaceutical ingredients and finished pharmaceutical products,
https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1010-annex10-who-stability-testing-of-active-pharmaceutical-ingredients.pdf?sfvrsn=7cb7a4c9_4&download=true
4. The International Pharmaceutical Excipient Council Significant Change Guide for Pharmaceutical Excipients.
5. The International Pharmaceutical Excipient Council Risk Assessment Guide for Pharmaceutical Excipients.
6. USP General Chapter <659> *Packaging and Storage Requirements*
7. Chinese Pharmacopoeia, General Chapter <251> *Pharmaceutical Excipients*
8. European Pharmacopoeia, Ph. Eur. 1. General Notices,
<https://www.drugfuture.com/Pharmacopoeia/EP7/DATA/10000E.PDF>
9. US FDA Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production - Level 2 revision,
<https://www.fda.gov/media/158416/download>
10. The International Pharmaceutical Excipient Council Composition Guide for Pharmaceutical Excipients.
11. IPEC Accelerated Aging Position Paper
12. USP, General notices "Storage temperature and humidity" (2nd Suppl.29-NF 24, p 3708), the calculation of a mean kinetic temperature, can be found in [Q1A\(R2\) Guideline.pdf](#) glossary reference for Mean kinetic temperature - Haynes calculation (J. D. Haynes, J. Pharm. Sci., 60:927-929, 1971).

13. CPMP/QWP/609/96/Rev 2, Guideline on Declaration of Storage Conditions,
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-declaration-storage-conditions_en.pdf
14. CPMP/QWP/4359/03 - EMEA/CVMP/205/04, Guideline on Plastic Immediate Packaging Materials, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-plastic-immediate-packaging-materials_en.pdf
15. The International Pharmaceutical Excipient Council Safety Guide for Pharmaceutical Excipients
16. IPEC-Americas Certificate of Analysis Guide for Bulk Pharmaceutical Excipients.