The IPEC Excipient Stability Program Guide

2010

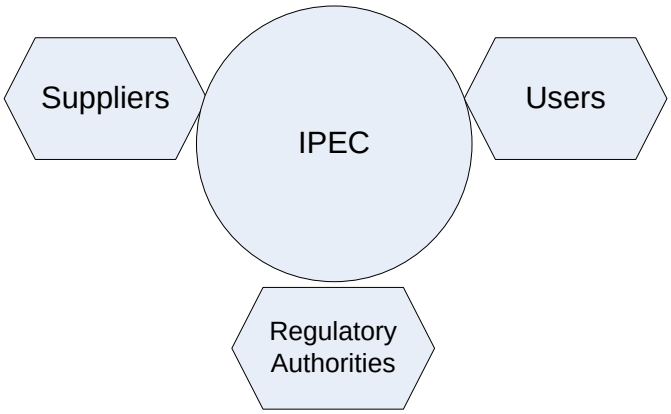
This document represents voluntary guidance for the pharmaceutical excipient industry and the contents should not be interpreted as regulatory requirements. Alternative approaches to those described in this guide may be implemented**.**

FOREWORD

IPEC is an international industry association formed in 1991 by manufacturers and end-users of excipients. It is an association comprising four regional pharmaceutical excipient industry associations covering the United States, Europe, China and Japan. IPEC's objective is to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace and the development of best practice and guidance concerning excipients.

IPEC has three major stakeholder groups;

1. Excipient manufacturers and distributors, who are considered suppliers in this document,
2. Pharmaceutical manufacturers, who are called users, and
3. Regulatory authorities who regulate medicines.



This document 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.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

This guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council, an industry association whose members consist of excipient manufacturers, distributors, and pharmaceutical users. The company representatives who worked on this Guide are listed below:

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1 INTRODUCTION

1.1 Purpose

The guideline is intended to provide excipient manufacturers with strategies for assessment of the stability of their excipients, and how this information may be disclosed to users and regulators. Since excipients are different from APIs and drug products, this document provides an appropriate guidance for developing supporting studies for excipients.

This guideline provides an approach for an excipient manufacturer to establish a stability study program for a pharmaceutical excipient. A suitable stability study should be used by the supplier to define reevaluation intervals or the expiration date. Studies may be used to support a Drug Master File (DMF) or Certificate of Suitability to the European Pharmacopoeia (CEP) filing, or to aid in the maintenance of supply chain quality and the product specifications. Conformance to this guide also gives confidence to the pharmaceutical end user that the excipient will continue to meet the excipient manufacturer's specifications or monograph requirements in the unopened container under the recommended storage conditions up to the retest/re-evaluation or expiry date.

1.2 Scope

This guide is applicable to all excipients including those that are new or novel chemical excipients. Note that in Europe when making a submission for a CEP, the EDQM only accepts stability data in accordance with ICH Q1A(R2)[1] if a retest interval is requested by the applicant on the certificate.

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".

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. This may result in some excipient stability data being supplied directly to regulators by the excipient manufacturer through mechanisms such as drug master files.

1.3 Principles Adopted

This guideline is intended to be of international application. As an international guideline, this document does not specify legal requirements nor cover particular characteristics of every excipient. This guideline acknowledges that the stipulations in ICH Q1A(R2) are not appropriate for excipients because ICH Q1A(R2) is intended for drug substances and drug

[1] ICH Q1A(R2), *Stability Testing of New Drug Substances and Products* http://www.ich.org/LOB/media/MEDIA419.pdf

products. However ICH Q1A can provide the principles of an excipient stability program but not the specific details.

1.4 Layout

This guide is divided into several sections. The General Guideline section provides guidance on establishing a stability study and communication of such information with excipient users and/or regulators. The final part contains definitions and references to other documents and websites useful in developing a stability program.

2 EXCIPIENT STABILITY PROGRAMS

2.1 General Guidelines

This guideline provides additional information to help with the implementation of the stability requirements in the IPEC-PQG GMP Guide and the IPEC GDP Guide[2].

The primary purpose of an excipient stability study is to provide evidence that the excipient will continue to meet specifications from the point at which manufacture has been completed (typically after packaging) and up to the point at which the package is opened. Any stability issues subsequent to opening the package are the responsibility of the user or any party carrying out re-packaging processes.

As noted in the IPEC-PQG GMP Guide for excipients available in multiple grades, bracketing and matrixing studies may also be appropriate[3].

Where excipients require specific storage conditions to preserve their quality during the retest/re-evaluation interval in the market package, the storage conditions required should be stated on the label and/or other literature, e.g. Excipient Information Package[4] or Certificate of Analysis[5]. Data should be available from the manufacturer to show these conditions are effective in assuring the conformance of the excipient to the excipient manufacturer's specification up to and including the retest/re-evaluation or expiry date. A suitable program for development of this data is described in this document. In case of very stable excipients (as discussed below), this guideline can still be used to provide evidence to that effect.

The stability of excipients varies. To foster communication between the excipient suppliers and users, their stability may be described as falling into one of several broad classifications based upon the stability of the excipient in their commercial package. These classifications are determined from existing stability data or an expert evaluation of the excipient based on its known chemical and physical properties.

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[2] See IPEC Good Distribution Practices Guide for Pharmaceutical Excipients 2006
[3] See ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products. http://www.ich.org/LOB/media/MEDIA414.pdf
[4] IPEC Excipient Information Package (EIP): Template and User Guide 2009
[5] IPEC-Americas Certificate of Analysis Guide for Bulk Pharmaceutical Excipients, 2000.

Very Stable

Very Stable excipients typically have the following attributes:

- The demonstrated history of stability in the specified packaging for at least 60 months (may be limited only by the durability of the packaging)
- Stability can be predicted based on their known attributes.
- Stability is not expected to be altered by changes in the manufacturing process.

For excipients classified in this category, with sufficient literature citations and/or stability studies to show the excipient remains unchanged for ≥ 60 months in relevant packaging, a further ongoing stability testing program is unnecessary. A statement or reference to a stability test in relevant packaging is all that is required to demonstrate stability to users. A summary report which includes pertinent data (e.g. stability indicating characteristics, literature citations, trending analytical results, storage condition monitoring) should be available to the user upon request.

Stable

Stable excipients typically have the following attributes:

- A retest/re-evaluation interval of at least 24 months but less than 60 months,
- Stability indicating characteristics (e.g. assay, marker impurities etc)
- Data to support the assigned retest/re-evaluation interval or expiration date

Such excipients have been demonstrated to be stable through literature citations and/or stability studies, but generally their stability is more sensitive to changes in the manufacturing process or product packaging than for excipients classified as Very Stable.

For excipients classified in this category, a statement or reference to a stability study in relevant packaging is all that is required to demonstrate stability to users. 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.

Limited Stability

Limited Stability excipients typically have the following attributes:

- Retest/re-evaluation interval or expiration date of less than 24 months,
- Stability indicating characteristics (e.g. assay, marker impurities etc),
- Limited stability data to support the retest/re-evaluation interval or expiration date.

Excipients classified in this category have stability characteristics that may be at higher risk from changes to the manufacturing process or product packaging.

Storage is typically under specified conditions in suitable packaging. 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.

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[1] 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.

Note that an excipient can be categorized in more than one classification depending on the protection given to it by the product packaging system. For example, while an excipient susceptible to oxidation whose 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. In this case justification of categorisation as very stable or stable on the basis of scientific data or historical evidence is required.

For new or novel chemical excipients, the classification may change during the development program as stability data becomes available.

Where there are no literature references to support classification as a Very Stable excipient or where the excipient meets the criteria for Stable or Limited Stability, then at least one stability study should be conducted using the intended commercial package/closure system (or surrogate) or alternatively a package which matches the commercial packaging as closely as possible. Ideally, this alternative package should be no more protective than the commercial packaging so that the study does not create a false assurance of excipient stability.

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.

For Stable or Limited Stability excipients, if a change occurs either in the process or with the packaging (container closure system) that may affect the excipient stability, a new stability study should be required. If the new package can be shown to be equivalent or better through other studies (e.g. moisture vapour permeation, or oxygen permeation), a new stability study may not be required to show the impact on excipient stability. 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.

It is expected that the excipient manufacturer or distributor who is re-packaging the excipient will have an agreement with packaging material suppliers requiring them to notify the excipient supplier of all significant changes to the packaging material.

2.2 Stability Studies:

There are various options available including the three below for design of an excipient stability study.

1. Utilize historical data including that found in the literature and generate a report summarising 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, and where the temperature of the warehouse is known and monitored,
3. Conduct a study using the conditions and recommendations in ICH Q1A(R2).

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. There should be evidence of the time intervals between the testing. If available, there should be evidence of the storage conditions used. The product packaging container/closure system should be defined, and the general conditions under which the samples or containers are stored should be known. A warehouse mapping/monitoring 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.

Examples of suitable historical data could include:

- An excipient that had been stored in a warehouse for three years and was retested after the storage period, and the results confirmed that the product was still within the specification.

- Documented evidence that product still has the desired functionality as an excipient after a defined period of time.
- Published data, public and internal to the company (e.g. poster presentations, journal articles, etc.) can be cited.

Options 1or 2 are particularly useful when no formal ICH study is required, and are expected to apply to most excipients. 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).

It is recognized that an excipient can be stored under uncontrolled warehouse conditions, unless labeling indicates otherwise. 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, 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

The aim of the stability study should be to provide evidence that the excipient is stable under the likely storage conditions. Uncontrolled warehousing conditions vary with geographical location, particularly with latitude. If the excipient is shipped to geographical locations which have storage conditions well outside the conditions used in the stability study, then additional studies may be required to show stability at these conditions. A warehouse monitoring program should be established if these conditions are not known.

The mean kinetic temperature can be used to assess the impact of variations in temperature, outside those normally experienced in the uncontrolled warehouse. on the excipient[6] and to support temperature limits indicated on the labels.

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.

Where the stability study indicates conditions which should be avoided then these should be specified on the label. Any specific protection requirements should also be stated on the label, e.g. ‘Protect from light’. The use of the terms Normal or Ambient are not recommended as they are ambiguous.

2.3 Stability Protocols

[6] USP, General notices "Preservation, Packaging, Storage and Labeling" (*USP-NF*), the calculation of a mean kinetic temperature, can be found in ICH Q1A; http://www.ich.org/LOB/media/MEDIA419.pdf referenced Haynes calculation (J. D. Haynes J. Pharm. Sci., 60:927-929, 1971): http://www.ikev.org/haber/stabilite/kitap/29%201.1%20Stability%20Workshop%20ICH%20Q1AR2%20C.pdf

The stability program 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,
- Selection and justification of batches (e.g. typical of production),
- Selection and justification of the container and closure system as the worst case,
- Storage conditions,
- Sampling plan,
- Selection and justification of stability indicating parameters
- Stability test methods.
- Methodology for the evaluation of acquired data
- Acceptance criteria,
- Approval process, and
- Interim and Final Report Content

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 on-going stability confirmation.

Scope:
The protocol should clearly indicate which excipient or grade of excipient are covered by the stability study, especially where the protocol is applied to a "model product" study[7] or a matrix design is used[3].

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 appropriate where more batches are unavailable. A single batch is typically appropriate for a continuing stability program.

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.

Selection and justification of representative batches
The selected batches should cover the normal production range (including Filling/Packaging), or at least the worst case in terms of specification parameters, particularly the stability-indicating parameters.

Selection of packaging for stability studies:

[7] The Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006.

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

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.

Storage Conditions:
The stability package should be stored under the specified storage conditions as defined in the protocol, or the conditions found in the manufacturer's warehouse. The stability study should be conducted over the longest period of time 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 period in excess of the duration of the stability study should be scientifically 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 hydrolyzes 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 for Stable and Limited Stability excipients, if a change occurs that may affect the excipient stability (for example in the process or with the packaging or container closure system).

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 retest/re-evaluation interval, for example samples may be tested at 0, 3, 6, 9, 12, 24 and 36 months.

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 container closure system 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 of the excipient in a container closure system that simulates the bulk package. This facilitates the retrieval of samples for testing without affecting the remaining excipient being stored for future stability testing. For excipients that require special storage considerations i.e. inert atmosphere or low humidity, etc., the protocol should take this into account if the sampled package is to be returned to stability storage.

The protocol should specify the frequency, from the date of manufacture[8] (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 degradation, if any, is slow enough to allow the excipient to remain within specification for its stated expiry date or retest/re-evaluation interval. 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.

Stability Indicating 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 stability indicating test or tests that demonstrate changes to the product. Ideally such changes should be determined using a method that yields a quantitative result.

The stability of excipients having a stability indicating assay method can be monitored using that 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

[8] IPEC-Americas Certificate of Analysis Guide for Bulk Pharmaceutical Excipients, 2000.

profile[9] of the excipient at the limit of its retest/re-evaluation interval, if appropriate, to that of the excipient at time zero. The composition profile of the excipient should remain essentially unchanged within the recommended storage conditions.

Out of Specification Results:
During a formal study, unexpected results may occur that are Out of Specification (OOS) or Out of Trend (OOT). These instances should be treated following a formal out of specification procedure[10]. 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 some time later in the study and thus an investigation may not be promptly initiated.

Methodology for the evaluation of acquired data:
The methodology to be used for evaluation of stability data to determine the excipient stability should be selected and defined in the protocol. In some cases, especially when there are no relevant degradation products formed, or product purity is not significantly influenced during storage, a simple comparison of stability data against product specification limits / acceptance criteria can be sufficient[11].

Acceptance Criteria:
The protocol should establish the limits for test results that are required to support the stated retest/re-evaluation interval. For each test parameter, an acceptance range should be specified. Trend analysis of the data should be used as an indication that the excipient will continue to meet specification through its retest/re-evaluation interval.

When defining the acceptance criteria in the protocol, additional testing beyond the product specification may be appropriate (e.g. chemical, physical, or performance changes).

Where a stability study identifies degradation products then consideration should be given to include these in the excipient specification.

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.

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[9] IPEC Excipient Composition Guide 2009.
[10] See IPEC-PQG GMP Guide Section 8.2.4.3
[11] More detailed guidance on the approach to evaluate data from quantitative attributes can be found, e.g. ICH Q1E, Pharmaceutical Analytical Sciences Group in the UK: http://www.pasg.org.uk/excel.htm, 1999, or other acceptable techniques.

2.4 Stability Reports:
After the data have been collected and evaluated against the acceptance criteria, a final report should be prepared. The report should contain an evaluation of the stability data and the conclusions reached and it should list and justify any deviation from the stability protocol.

A summary report should be prepared in a format for presentation to users or to support regulatory submissions. A summary report for communication outside the Company may be appropriate. Summary reports may be the subject of a Confidential Disclosure Agreement.

The report should define the excipient grade(s) and packaging type(s) for which the stability data is applicable, the recommended storage conditions, the stability-indicating characteristics and their acceptance criteria, the retest/re-evaluation interval for the excipient, and, where the data indicates it, the expiry interval. Batches of excipient may then be subjected to retesting if they have been stored within the defined conditions in the unopened package beyond the retest/re-evaluation date, and if the batch is within the expiry interval.

3 DEFINITIONS AND GLOSSARY

Active Pharmaceutical Ingredient (API): Any substance or mixture of substances, intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body of man or animals.

Certificate of Analysis (COA): A document listing the test methods, specifications and results of testing a representative sample from the batch to be delivered.

Certificate of Suitability to the European Pharmacopoeia (CEP): Certification granted to individual manufacturers by the European Directorate for the Quality of Medicines (EDQM) when a specific active ingredient or excipient is judged to be in conformity with a Ph. Eur. monograph and that the monograph is adequate to control the material.

Change: Anything that alters an excipient's physical, chemical and/or microbiological characteristics from the norm, or that is likely to alter the excipient performance in the dosage form.

Component: Any material present in the excipient that arises as a consequence of the raw materials and/or manufacturing process.

Composition Profile: A description of all of the components present in the excipient.

Date of Manufacture: A date indicating the completion of the final manufacturing process (as defined by the supplier for the particular excipient and process).

Drug Master File (DMF): Detailed information about the manufacture of an excipient that can be submitted to regulatory authorities such as the United States Food and Drug Administration, Health Canada, and the Japanese Pharmaceutical and Medical Devices Agency.

Excipient: Substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

Expiry (Expiration) Date: The date designating the time up to which the excipient is expected to remain within specifications and after which it should not be used.

Expiration Period: The duration, normally expressed in months or years from the date of manufacture, within which the excipient can continue to be used.

Functionality: A desirable property of an excipient that aids manufacturing and improves the manufacture, quality, or performance of the drug product.

Good Manufacturing Practices: Requirements for the overall quality system under which drug products and their ingredients are manufactured, tested, and released. Current Good Manufacturing Practices (cGMP) is the applicable term in the United States. For purposes of this guide, the terms GMP and cGMP are equivalent.

Out of Trend (OOT). A result that is not expected based on an examination of previous data when presented in chronological order, but remains within specification. A result showing a distinct offset from the rest of the data set**.**

Packaging Material: A material intended to protect an intermediate or excipient during storage and transport.

Process: The set of operating steps including synthesis, isolation, purification, packaging, etc. that produce the finished excipient.

Protocol: A detailed plan describing the conduct of a study.

Retest/re-evaluation Interval: The duration, normally expressed in months or years, from the date of manufacture, throughout which the excipient should continue to conform to the specification and after which should be tested to confirm it continues to meet specification.

Retest Interval: (see Retest/re-evaluation Interval)

Shelf Life: The length of time during which the excipient meets specification (see also expiration period, retest/re-evaluation interval and retest interval).

Specification: A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described for a material, that the material is required to meet.

Stability Test Method - A test that investigates whether or not a particular characteristic of the excipient changes relative to specification over time.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Worst Case: A set of conditions encompassing processing limits, circumstances, equipment, etc., which pose the greatest chance of a failure in a process, to a product, or in a procedure, when compared to ideal conditions or those stipulated in a procedure. Such conditions do not necessarily induce product, process, or equipment failure.

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