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Step 2b

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

STABILITY TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q1

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ICH HARMONISED GUIDELINE

STABILITY TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q1

ICH CONSENSUS GUIDELINE

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1 INTRODUCTION

1.1 Objectives of the Guideline

The following guideline outlines the stability data expectations for drug substances and drug products. This guideline is applicable to marketed drug products, including those associated with registration and lifecycle/post-approval changes and, when applicable, master files. These applications are hereafter collectively referred to in the guideline as regulatory submissions. ICH Q1 is a consolidated revision that supersedes ICH Q1A-F and Q5C guidelines and provides additional guidance on principles relating to stability.

1.2 Scope of the Guideline

This guideline applies to synthetic and biological drug substances and drug products, including the following:

- Chemically synthesised drug substances including oligonucleotides, polysaccharides and polypeptides (collectively referred to as 'synthetic chemical entities' or 'synthetics' in this guideline), semi-synthetic drug substances and fermentation-derived drug substances.
- Therapeutic proteins/polypeptides, polysaccharides and proteoglycans produced using recombinant DNA (rDNA) technology or isolated from human, animal or plant tissues, other natural sources, including body fluids (such as plasma-derived products), or cell cultures.
- Conjugated products that are made up of proteins/polypeptides linked to another moiety (e.g., antibody-drug conjugate).
- Vaccines, allergenic products, and adjuvants.
- Autologous and allogenic cell-based substances, including those which may be genetically modified *ex-vivo* (refer to Annex 3 – Stability of Advanced Therapy Medicinal Products (ATMPs)).
- Gene therapy products that mediate their effect by the expression (transcription or translation) of transferred genetic materials and genome editing products used to modify cells (refer to Annex 3 – Stability of Advanced Therapy Medicinal Products (ATMPs)).
- The drug constituent part of a combination of a drug product with a medical device (both integral or co-packaged).
- Co-packaged solvents/diluents.
- Natural health products that are regulated as drug products.

The guideline is applicable to all regulatory submissions and, in accordance with regional regulations, can apply to prescription and non-prescription drug products (e.g., regulated over-the-counter products), original drug products (e.g., new entities), new product presentations, abbreviated/abridged applications (e.g., generics) and biosimilars.

The principles outlined in this guideline are applicable to support post-approval changes (PACs) that require supportive and confirmatory stability studies, including those that are discussed within ICH Q12.

Although this guideline is not directly applicable to drug substances and drug products during clinical development stages, the concepts can apply proportionate to increasing level of product and process understanding during pharmaceutical development. The data from development batches that meet primary stability requirements may be used to support a regulatory submission and for product lifecycle management. Refer to Section 15 - Stability Considerations for Commitments and Product Lifecyle Management.

The guideline is not applicable to device constituent parts, radiopharmaceuticals and whole blood products.

1.3 Introduction to Guideline and General Principles

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental and physical factors such as temperature, humidity, light, or agitation. Stability testing establishes and confirms a re-test period or shelf life for the drug substance or a shelf life for the drug product in the proposed container closure system under the recommended storage conditions. Shelf life is also referred to as dating period or expiry period in some regions. This guideline provides comprehensive guidance to establish stability for all molecule types within its scope and includes recommendations on how science- and risk-based principles may be applied. A standard approach to assess each stability-related topic is provided by describing the general principles and strategies to assess stability. In addition, the principles of Quality by Design described within ICH Q8-Q11 and Q14, through enhanced understanding of critical quality attributes (CQAs) and the impact that the manufacturing process can have on these attributes, are applicable to the design of an overall stability strategy.

This guideline should be considered in its entirety for a comprehensive approach to stability studies.

The guideline exemplifies the standard stability data package for drug substances and drug products and provides guidance on alternative and scientifically justified approaches that encompass the variety of different situations that may be encountered due to specific scientific considerations and

characteristics of the data being evaluated. Alternative strategies based on science- and risk-based principles (e.g., as described in ICH Q8-Q11 and section IX of ICH Q12) for drug substances and drug products may be proposed by the applicant of a regulatory submission, leveraging quality risk management principles, pharmaceutical development data (e.g., as discussed in Section 2 – Development Studies Under Stressed and Forced Conditions), prior knowledge and modelling, (e.g., as discussed in Annex 2 -Stability Modelling). Examples are provided under specific sections to illustrate how science- and risk-based strategies may be applied.

Unless otherwise specified, the recommendations described in this guideline apply to both drug substance and drug products. Additionally:

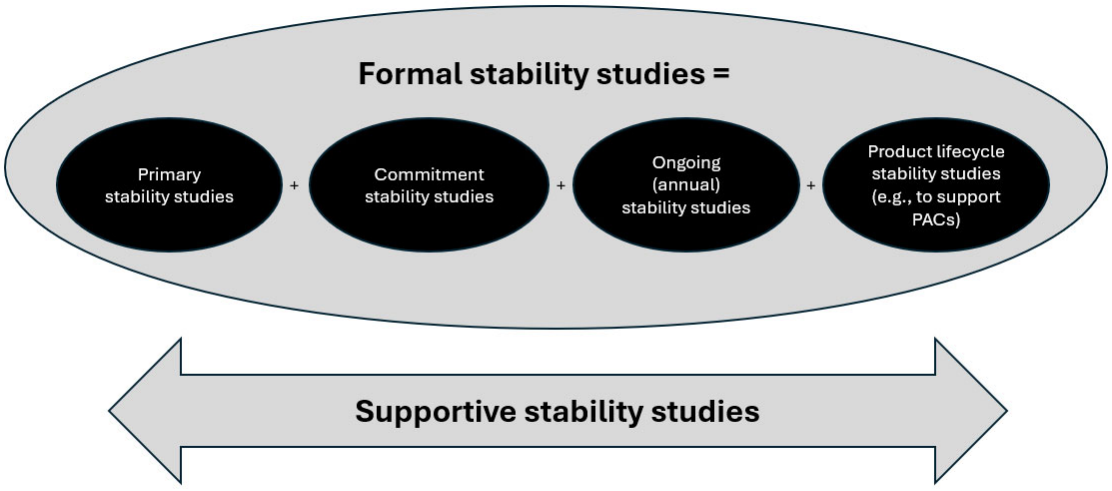
- Each section may include guidance for specific product types (e.g., synthetics, biologicals, vaccines or a combination drug product with a medical device) where relevant.
- For semi-synthetics, fermentation and conjugated products, the recommendations for synthetics and biologicals would apply, as appropriate.
- Where “products” is mentioned by itself in this guideline, this is to be interpreted as “drug substances and drug products”.
- Recommendations on the general principles for stability studies and data expectations for drug substances and drug products apply across all climatic zones for regulatory submissions and lifecycle management. The mean kinetic temperature in any part of the world can be derived from climatic data, which divides the world into four climatic zones, I-IV (13, 14). The four zones are distinguished by their characteristic prevalent annual climatic conditions based on the concept originally described by W. Grimm (15), updated in W. Grimm (16) and adopted under WHO Technical Reports (13, 14). This guideline addresses all four climatic zones. The principle has been established that if the stability information is generated under a more severe climatic zone storage condition, it would be acceptable in the other climatic zones, provided the information is consistent with this guideline and the labelling and storage statements are in accordance with regional requirements.
- The recommendations may be applicable to drug substance intermediates and drug product intermediates. Intermediates that are stored as part of manufacturing process activities (e.g., unprocessed bulk harvest, granulations) should be evaluated in accordance with Section 9 - Stability Considerations for Processing and Holding Times for Intermediates. For those intermediates that are packaged and stored outside of manufacturing process activities, a holding time may be established or it may be appropriate to establish a re-test period or shelf

life as per the applicable sections of this guideline (e.g., antibody prior to conjugation and a spray dried dispersion).

- The recommendations may be applicable to reference materials as well as to drug products containing certain excipients and adjuvants where the stability of these components can significantly impact drug product performance. Refer to Section 12- Reference Materials, Novel Excipients and Adjuvants for detailed guidance. Co-packaged solvents/diluents should follow the recommendations for drug products.
- Regulatory expectations for the stability data package in this guideline are also applicable to drug substances and drug products made using continuous manufacturing (CM) processes.
- Annexes are intended to either supplement the guideline with specific guidance on enhanced approaches or to provide product-specific guidance for product types with specific and unique stability considerations. Annex 1 provides guidance on Reduced Protocol Design; Annex 2 provides guidance on Stability Modelling; and Annex 3 provides Additional Considerations for ATMPs.

The main types of stability studies are graphically represented in Figure 1.

Figure 1: Stability Study Types



Formal stability studies are primary, commitment, ongoing and product lifecycle stability studies conducted under the accelerated, intermediate, or long-term storage conditions (as applicable) to establish or confirm a re-test period or a shelf life. Supportive stability studies are those stability studies that are conducted (as applicable) to support the practical use of the product (including label claims) or a re-test period or a shelf life (e.g., photostability, in-use, short-term storage condition studies and

studies to support excursions or modelling). Formal and supportive stability studies and their purposes are described in various sections of this guideline. In addition to formal stability studies, guidance is provided on studies that inform stability knowledge and product understanding (refer to Section 2 – Development Studies Under Stressed and Forced Conditions). These development studies are introduced in Section 2 because some of this information is utilised to develop the primary stability protocol and the validation of stability-indicating methodologies.

The guideline discusses strategies for protocol design within Section 3 - Stability Protocol Design to Section 7 - Storage Conditions. The recommendations in these sections are applicable to primary stability studies. However, the principles of protocol design are intended to apply to any stability protocol (e.g., commitment, ongoing and product lifecycle stability studies, including those to support changes).

The concept of a 'representative batch' to support establishing the re-test period or shelf life is referenced throughout this guideline. The justification that a batch is representative will vary depending on the drug substance and drug product types, their complexity and manufacturing processes. This is discussed in detail within Section 4 - Selection of Batches.

The applicant should consider all available stability knowledge when designing stability protocols and defining information for inclusion on the product labelling (e.g., storage statements). This includes considerations of the impact of holding times, the primary stability data and supportive stability data to inform long-term, short-term and in-use storage conditions. In many cases, stability protocol designs may be dependent on the potential impact on the final product quality and therefore based on quality risk management.

This guideline does not specify filing mechanisms or regional requirements.

2 DEVELOPMENT STABILITY STUDIES UNDER STRESS AND FORCED CONDITIONS

Product knowledge is useful in the design of formal stability study protocols. Development studies may be useful to characterise the physical, chemical and biological changes likely to occur with storage, to establish the degradation profile and intrinsic stability of the product, to confirm and validate the stability-indicating nature of the analytical procedures, to inform specifications and to determine whether unexpected exposures to conditions other than those defined in the label are deleterious to the product (refer to Section 14 – Excursions Outside of a Labelling Claim). In addition, these development studies can be used to help design the primary stability protocol and may also be applied to protocols used to support changes during the product lifecycle (refer to Section 3 - Stability Protocol Design and Section 15 - Stability Considerations for Commitments and Product Lifecyle Management).

In the context of generating product knowledge, studies may be performed under accelerated and/or stress conditions, including forced conditions. The nature of this testing should be proportionate to the knowledge available, the type of the drug substance or drug product being evaluated and the quality attribute(s) being investigated.

Accelerated conditions (temperature and when applicable, humidity), over a defined time period, are intended to increase the rate of chemical degradation, physical change and/or biochemical change in the product. Data generated under accelerated conditions can be used to gain product knowledge and to support extrapolation, re-test or shelf life determination and to evaluate the impact of excursions outside the label storage conditions. Accelerated testing is typically included as part of the formal stability program as described in Sections 3 – Stability Protocol Design through Section 7 – Storage Conditions.

Development studies undertaken to assess the effect of stress on the drug substance and/or drug product can be divided into two categories:

1) Studies conducted under *stress conditions*: Conditions are more severe than the accelerated conditions but not necessarily intended to deliberately degrade the sample.

2) Studies conducted under *forced degradation conditions*: Conditions are intended to deliberately degrade the sample (such as elevated temperature, humidity, pH, oxidation, agitation and light).

The purpose of this section is to describe the principles of development studies under stress and forced conditions. This section provides clarity on the concepts, study design and considerations for interpreting the results.

2.1 Development Studies Under Stress Conditions

Studies under stress conditions can contribute to an understanding of product knowledge and the data gathered from these studies can be useful in addressing unexpected excursions outside of the conditions defined on the labelling (refer to Section 14.1 – Excursions Outside of a Labelling Claim).

Stress condition studies can include temperature and humidity levels above accelerated conditions, thermal cycling and freeze-thaw studies, as appropriate. For synthetic chemicals entities, these studies may be conducted on one batch of the drug product and where relevant one batch of the drug substance directly exposed or in a container closure system, as applicable. For biologicals, at a minimum, stress studies may be performed on a single batch of drug product, however, it may be possible to justify using a single batch of drug substance if it is representative of the drug product.

2.2 Development Studies Under Forced Degradation Conditions

Forced degradation studies may be utilised to investigate potential degradation pathways; gain product knowledge; understand the intrinsic stability of product and used to develop and confirm stability-indicating nature of the analytical procedure (refer to ICH Q2 and ICH Q14). It is acceptable to leverage product knowledge when data is available on identified degradation products and pathways, including scientific literature.

It is recommended to assess forced conditions on a single batch of the drug substance. It should include the effect of elevated temperatures, humidity (e.g., 75% Relative Humidity (RH) or greater) where appropriate, oxidation and photodegradation on the drug substance. Testing should evaluate the susceptibility of the drug substance to hydrolysis across a range of pH values. Also, a combination of forced conditions may be appropriate to test under certain circumstances (e.g., agitation and heat).

For drug products, testing under forced conditions is recommended on a single batch of exposed drug product. It should include the effect of temperature, humidity (e.g., 75% RH or greater) where appropriate and light. Additional forced conditions for specific types of products and dosage forms may be appropriate.

For biologicals, studies under forced degradation conditions should be performed on a single batch of drug substance; alternatively, it may be possible to justify using a single batch of drug product.

The forced photodegradation condition can be an integral part of forced degradation studies. The purpose of forced photodegradation studies is to evaluate the overall photosensitivity of the product. A forced photodegradation study requires exposure to light conditions which are more extreme than the light conditions utilised in confirmatory studies (refer to Section 8 – Photostability).

With forced degradation studies, the conditions and duration may need to be varied depending on the sensitivity of the product. For development and analytical procedure validation purposes, it is appropriate to limit the exposure and end the forced degradation study if extensive decomposition occurs. Similarly, for stable materials, studies may be terminated after an appropriate exposure level has been used. The design of these experiments is left to the applicant's discretion although the exposure levels used should be justified.

2.3 Analysis and Interpretation of Results

When testing under stressed conditions, including forced degradation, samples should be examined at the end of the exposure period for any changes in physical, chemical, or biological properties (e.g., physical state, clarity, colour, degradation products, particle size, potency), as applicable, by a procedure suitable to detect any evidence of change.

Changes in attributes that are unlikely to occur under normal storage conditions may occur under forced conditions and possibly under stress conditions (e.g., the formation of degradation products). This information may be useful in developing and validating suitable analytical procedures and can be part of a comprehensive approach to justify the overall control strategy.

The data obtained from these development studies may also inform product understanding and help identify the potential stability-indicating CQAs that should be monitored during stability testing, assisting in the design of the stability protocol (refer to Section 3 - Stability Protocol Design). Although forced degradation studies are not part of the formal stability studies, results from the forced degradation studies are an integral part of the information provided to regulatory authorities (e.g., support analytical procedure validation, product characterisation, specifications or packaging considerations). Data from development studies under stress condition should be included in regulatory submissions if they support a claim on the product labelling.

3 PROTOCOL DESIGN FOR FORMAL STABILITY STUDIES

This section provides guidance that is intended to be used in conjunction with Section 4 – Selection of Batches through Section 7 – Storage Conditions to establish a formal stability study protocol. Figure 2 illustrates how an applicant may approach the design and development of a formal stability protocol. The “available stability data” in the figure refers to knowledge gained from long-term and accelerated stability studies conducted earlier in development and from development studies discussed in Section 2 – Development Studies Conducted on Stressed and Forced Conditions.

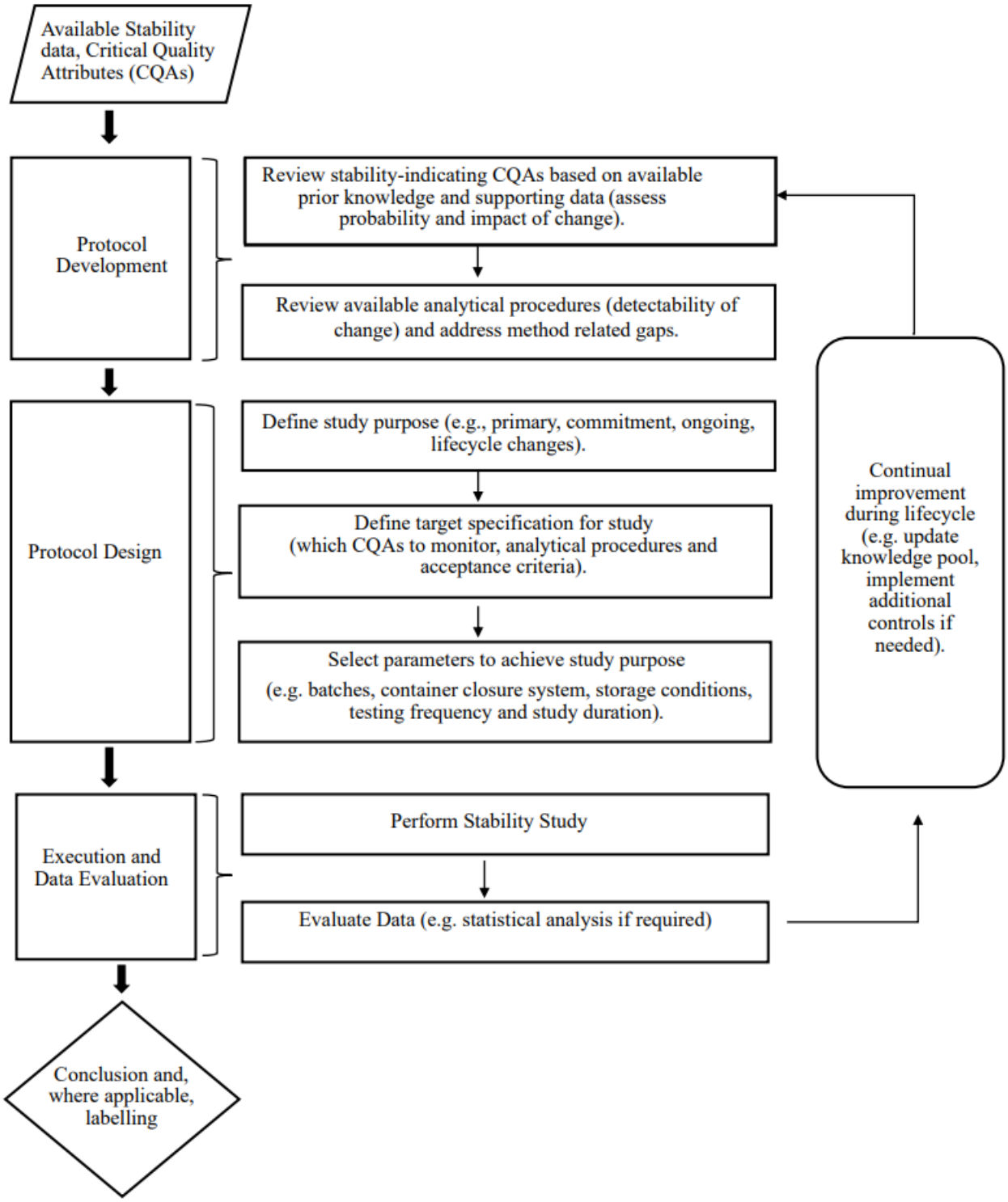
Where noted, these sections provide specific guidance for establishing a primary stability protocol to determine a re-test period or shelf life (refer to Section 13 - Data Evaluation). When applicable, the guidance in these sections should be utilised in conjunction with Section 15 - Stability Considerations for Commitments and Product Lifecyle Management (for commitment stability studies, ongoing stability studies and lifecycle stability studies) and Annex 1 - Reduced Stability Protocol Design (where reduced study designs may be appropriate).

3.1 General Principles

A summary of the stability protocol should be provided in a regulatory submission when a re-test period or shelf life is to be established or confirmed. The stability protocol incorporates all necessary information to establish or confirm the stability of the drug substance or drug product under the recommended storage conditions throughout the re-test period or shelf life. This includes consideration of data from primary stability studies and supporting data to inform long-term storage, short-term storage, excursions and in-use conditions.

An illustration of the general process for the development, design and execution of a stability protocol is shown in Figure 2. The applicant is responsible for building knowledge and understanding during pharmaceutical development, leading to the identification of those CQAs that are or have the potential to be stability-indicating under appropriate storage conditions and using this information to design the protocol to support the formal stability studies. Stability studies should include testing of those attributes that are susceptible to change during storage and can potentially influence quality, safety and efficacy. During the product's lifecycle, as knowledge is gained, stability protocol designs may be optimised. Changes to the stability protocol to extend a re-test period or shelf life should be established in accordance with Section 15 - Stability Considerations for Commitments and Product Lifecyle Management.

256 **Figure 2**: **General Process Flow for the Development, Design and Execution of a Stability Protocol**



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The principles detailed for protocol design should be applied from initial regulatory submission through product lifecycle. The precise protocol design will depend on the drug substance/drug product, study purpose and the available prior knowledge.

Additional protocol considerations for photostability, excursions, short-term storage and in-use conditions are described in the respective sections (refer to Section 8 – Photostability, Section 14.1 – Excursions Outside of a Labelling Claim, Section 10 - Short-Term Storage Conditions and Section 11 – In-Use Stability).

A full design stability protocol is a protocol where at least three batches of the drug substance or at least three batches of each strength of the drug product covering the proposed container closure systems for every combination of all design factors are included and tested at all time points. Alternative approaches to stability protocol design, such as bracketing, matrixing, knowledge- and risk-based protocol reductions and stability models are described in Annex 1 – Reduced Stability Protocol Design and Annex 2 – Stability Modelling. Additional considerations for ATMPs are provided in Annex 3 – Stability of Advanced Therapy Medicinal Products (ATMPs).

3.2 Stability Data to Support the Initial Re-test Period and Shelf Life According to the Standard Approach

This section provides guidance on establishing the re-test period, shelf life and storage conditions using data from the primary stability study (refer to Section 4 – Selection of Batches). This is considered the standard approach. When the standard approach is adopted, the recommendations provided in Table 1 establish an appropriate minimum dataset at the time of the initial regulatory submission to assign a re-test period and shelf life in accordance with the guidance provided in Section 13 – Data Evaluation. Alternative approaches to the principles and practices described in this section may be acceptable if they are supported by adequate justification, including an enhanced knowledge of product performance from prior knowledge, as per ICH Q8 - Q11 and modelling as discussed in Annex 2 - Stability Modelling.

The stability package provided in the regulatory submission should be sufficient to support the proposed re-test period or shelf life and storage conditions. The long-term stability protocol should, at a minimum, ensure testing continues for the duration of the proposed re-test period or shelf life.

Data from the accelerated storage conditions and, if appropriate, from the intermediate storage conditions can be used to evaluate the effect of short-term excursions outside the labelled storage conditions (e.g., during shipping). For synthetics, data from the accelerated storage condition are also needed to enable extrapolation in accordance with Section 13.2.5 – Extrapolation for Synthetic Chemical Entities. For biologicals, data from the accelerated storage condition is utilised for product

understanding and may be used to support analytical comparability. Even though data generated under accelerated storage conditions are not used to establish a re-test period or shelf life for biologicals, it is strongly suggested to include these data in the regulatory submission.

Refer to Section 4 – Selection of Batches, Table 2 for guidance on selection of primary batches. For synthetics and for biologicals, a primary batch may be a production batch but does not need to be a production batch.

Biological drug substances and drug products usually require stringent conditions for their storage to ensure maintenance of biological activity and to avoid degradation, because of dependence of molecular conformation and biological activity on noncovalent as well as covalent forces, resulting their high sensitivity to environmental factors (e.g., temperature changes, oxidation, light, ionic content and shear). The evaluation of their stability may necessitate complex analytical methodologies including physicochemical, biochemical and immunochemical methods, and consideration of many external conditions which can affect the product's potency, purity and quality. For biological drug substances and drug products, data from three primary batches that cover the duration of the proposed shelf life should be submitted unless an alternative approach is justified. When these primary batches are not production scale, a minimum of 6 months of data from production batches should also be submitted to support the evaluation of the regulatory submission. A minimum of 6 months stability data from primary batches should be submitted in cases where shelf life is greater than 6 months. For drug substances and drug products with a shelf life of less than 6 months, the minimum amount of stability data in the initial regulatory submission should be determined on a case-by-case basis. Refer to Section 15 - Stability Considerations for Commitments and Product Lifecyle Management for guidance on providing commitment stability data after marketing authorisation.

A stability study to establish a re-test period or shelf life should include at least three batches of the drug substance or at least three batches of each strength of the drug product covering the proposed container closure systems. Reduced designs may be applied where justified (refer to Annex 1 – Reduced Stability Protocol Design).

For synthetic chemical entities and biologicals, if primary batches are not production scale or not all at production scale, the applicant should commit to continuing or initiating and completing a commitment stability study to establish and confirm the re-test period or shelf life in accordance with Section 15.1 - Commitment Stability Studies.

323 **Table 1: Recommended Core Stability Data for the Standard Approach at Submission to**
324 **Support the Initial Re-test Period or Shelf Life[1]**

Product Type	Batch Type	Number of Batches[2]	Long-term storage condition	Accelerated storage condition
New synthetic chemical entity drug substances and/or drug products for which a new drug regulatory submission is required[4]	Primary[5]	3	12 months	6 months[3]
Existing synthetic chemical entity drug substances and/or drug products for which an abbreviated/ abridged regulatory submission is required	Primary[5]	3	6 months	6 months[3]
Biological drug substances and/or drug products	Primary, Production[5]	3	6 months [6]	6 months[7]

[1] For testing frequency guidance refer to Section 6 – Testing Frequency

[2] For a full design, at least 3 batches of the drug substance or at least 3 batches of each strength of the drug product covering the proposed container closure systems are tested. Reduced designs may be applied where justified (refer to Annex 1 – Reduced Stability Protocol Design).

[3] If a significant change (refer to Section 13 - Data Evaluation) or an out of specification result occurs at accelerated conditions within the first 3 months, it is considered unnecessary to continue to test through 6 months.

[4] In principle, stability protocols for new dosage forms and new strengths/concentrations should follow the guidance for a new drug. However, a reduced stability dataset at submission time (e.g., 6 months accelerated and 6 months long term data) may be acceptable in certain justified cases (refer to Section 15.3 - Stability Studies to Support New Dosage Forms and New Strengths/Concentrations).

[5] There should be a commitment to continue stability studies for production batches corresponding to the proposed re-test period or shelf life.

[6] A primary batch can be a production batch but does not need to be a production batch. If the re-test period or shelf life proposed from non-production primary batch data is greater than 6 months, stability data from production batches should be a minimum of 6 months. The shelf life would generally be supported by three primary batches having stability data through to shelf life.

[7] Testing under accelerated storage conditions is strongly suggested when appropriate for the storage condition and product type and the minimum time period should be justified by the applicant in accordance with the selected storage conditions. A minimum of three time points, including the initial and final, is recommended.

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For drug substances and drug products with intended storage periods of less than the recommendations in Table 1, the minimum amount of stability data in the initial regulatory submission should be determined based on the product-specific risks and in accordance with Section 6 – Testing Frequency.

3.3 Stability-Indicating Critical Quality Attributes

CQAs should be identified using the principles outlined in ICH Q6A, Q6B and ICH Q8-Q11. When designing a stability protocol in support of a drug substance or drug product, information on the CQAs and their target acceptance criteria should already be available. Based on prior knowledge and development data, the applicant should identify the stability-indicating CQAs, which are those attributes that may change upon storage and may impact the functionality and/or quality of the drug substance or drug product.

3.3.1 Recommendations for Establishing a Re-Test Period or Shelf life.

The stability protocol to establish a re-test period or shelf life should include stability-indicating CQAs and compile a suitable dataset to demonstrate product quality through storage and use. For synthetic chemical drug substances and drug products, the stability protocol should consider appropriate, physical and chemical attributes. For biological drug substances and drug products, the protocol should assess changes in CQAs that affect physicochemical properties, purity and impurity levels, immunochemical properties and the biological activity of the product, as appropriate. For both synthetics and biologicals, microbiological attributes and product performance characteristics should be confirmed on stability as applicable. For products that are particularly sensitive to changes in temperature, oxidation, light, moisture content and shear forces, quality attributes that may be impacted should be assessed. For additional information on attributes to be included in the drug substance or drug product specification, refer to ICH Q6A and Q6B.

Where excipient levels or their properties may change on stability, potentially impacting drug product CQAs, they should be evaluated as part of drug product stability testing, (e.g., levels of surfactant, preservative content). In cases where stabilisers are needed for a biological drug substance, the same considerations should be applied. Co-packaged diluents should follow the recommendations for drug products. A risk-based approach is recommended, where development data and excipient prior knowledge can be used to understand whether additional drug substance and/or drug product stability data are appropriate to support the re-test period or shelf life.

In accordance with the principles outlined in ICH Q3D and Q3E, stability-indicating CQAs considerations should include potential interaction with the respective storage container, contact with administration or delivery devices (e.g., syringe walls, catheters and injection needle) and dispersion media (such as solvents for reconstitution or dilution).

3.3.2 Recommendation for Lifecycle Stability Protocols

After additional knowledge is gained following establishment of the re-test period or shelf life, data may confirm that some CQAs do not change on stability and stability protocols to support the product lifecycle may be updated accordingly (refer to Section 15 – Stability Considerations for Commitments and Product Lifecyle and Annex 1 - Reduced Stability Protocol Design)

3.4 Specifications

3.4.1 Tests and Analytical Procedures

Before a formal stability study protocol is initiated, the suitability of the proposed analytical procedures to detect changes in the stability-indicating CQAs should be assessed in accordance with ICH Q2 and ICH Q14. The analytical procedures used to monitor changes in the stability-indicating CQAs should be chosen and validated to provide assurance that changes to product quality will be detected, measured and understood over the expected re-test period or shelf life. Establishment of potential degradation pathways (refer to Section 2.3 -Analysis and Interpretation of Results) is important when developing and validating suitable analytical procedures. When feasible for synthetic chemical entities, the mass balance relationship between tested attributes should be observed when selecting appropriate stability-indicating tests. For example, for solid drug substances or drug products, an apparent decrease in the active moiety could be caused by an increase in degradation products and/or an increase in moisture content.

When justified, the analytical procedures used for stability testing may differ from the release analytical procedure for the same quality attribute (e.g., container closure integrity testing may be used instead of sterility testing during stability). In situations where stability-indicating quality attributes are not tested as part of release testing (e.g., the relevant CQAs are measured and controlled during processing as described in ICH Q8), additional analytical procedures should be established to support stability studies.

3.4.2 Acceptance Criteria

The shelf life acceptance criteria should consider all available stability information from development and manufacture of the drug substance through final drug product shelf life in accordance with ICH Q6A and Q6B. As per these guidelines, when a stability-indicating CQA changes over time, it may be appropriate to establish a release specification that is more stringent than the shelf life specification to ensure that the drug substance and/or drug product quality is maintained through to the end of shelf life. In general, any differences between the release and shelf life acceptance criteria should be justified with data. In case a re-test period is assigned to a drug substance, generally the acceptance criteria are the same as at release.

3.4.3 Pharmacopoeial Critical Quality Attributes and Analytical Procedures

When drug substance and/or drug product monographs or general procedures are available and relevant to the region(s) where the regulatory submission is to be filed, the monographed CQAs and analytical procedures are an appropriate starting point in designing a product-specific stability protocol. Any differences in the proposed analytical procedures from those in the pharmacopeia should be scientifically justified (e.g., including demonstration of equivalency). A knowledge- and risk-based approach should then be applied to ensure that any differences in stability behaviour are properly controlled.

3.5 Additional Considerations for Vaccines

In cases where the potency of the product is dependent on conjugation and/or adsorption of the active ingredient to another moiety (e.g., carrier), applicants should evaluate potential dissociation of the active ingredient(s) from the carrier during storage (e.g., in conjugate vaccines).

In cases where the potency of the product is dependent on the inclusion of an adjuvant, the CQAs for the adjuvant should be evaluated during stability studies.

It is strongly recommended that stability studies for vaccines include mechanisms to evaluate the potency (i.e., the specific ability or capacity to achieve its intended effect using suitable methods) of the product.

3.6 Additional Considerations for the Combination of a Drug Product with a Medical Device

The stability of a combination of a drug product with a medical device considers (a) drug product CQAs and (b) drug device combination performance characteristics through storage to the completion of administration (refer to Section 11 – In Use Stability). The functional performance characteristics of the device constituent alone are outside of the scope of this guideline and are addressed through device design verification studies.

The stability protocol design for a combination of a drug product with a medical device (integral or co-packaged) should follow the same principles as described for a drug product, including a risk assessment and compatibility with contact materials. Stability-indicating attributes of the drug constituent may impact the medical device functional performance characteristics, and stability studies and conclusions should account for these interactions. Considerations should be made for the administration-dependent functional performance characteristics of the fully assembled combination of a drug product with a medical device that may be impacted by long-term storage (i.e., CQAs that can only be assessed after assembly). The storage orientation may be established based on a risk assessment. The shelf life of a co-packaged combination of a drug product with a medical device should be based on the shorter of

either the device constituent part or the drug constituent part shelf life. For integrated device-drug products, the shelf life should be based on the shorter of either of the constituent part or the final combination of a drug product with a medical device.

Each type of combination of a drug product with a medical device should have its own unique list of quality attributes and administration-dependent functional performance characteristics. Attributes should be risk assessed according to the specific design of that product to identify the critical attributes or characteristics. The risk assessment may include data from device design development studies and prior knowledge from similar combinations of a drug product with a medical device. The stability protocol should use the assembled (integral or co-packaged) product representative of the product proposed for marketing. If the stability studies were not performed with the combination of a drug product with a medical device as proposed for marketing, the changes made should be assessed and justified with respect to the impact on stability.

3.7 Risk Management

A science- and risk-based approach should be used to inform the different aspects of protocol design outlined in Section 4 - Selection of Batches through Section 7 - Storage Conditions.

The inclusion of risk management information with a registered stability protocol is not mandatory, but in cases where it forms the basis of a justification for enhanced/reduced protocol approaches, information on the risk assessment process, outcome and the connection to the stability protocol should be described.

4 SELECTION OF BATCHES

To establish a re-test period or shelf life for the drug substance and drug product, stability data should generally be provided on three primary batches. Alternative approaches for batch requirements may be supported when justified. The manufacturing process for the primary batches of drug substance and drug product should be similar or representative, but not necessarily identical to the manufacturing process used for production batches. Hence, a primary batch may be but is not necessarily a production batch. Differences in the manufacturing processes for the primary batches and those proposed for production batches should be justified. Specific considerations for primary stability batches are provided in Table 2.

For studies that are not a primary study (e.g., in-use stability, photostability, supportive studies and stability studies to support post-approval changes) and use non-production batches, the batches should be representative as described below:

- Synthetic chemical entities: Chemically synthesised drug substances should be manufactured by the same synthetic route. Changes to manufacturing process parameters should be scientifically justified. Drug products should be of the same formulation and method of manufacture.
- Biologicals: The quality of all drug substance and drug product batches placed in a stability program should be manufactured using a similar process to the proposed production manufacturing process and be analytically comparable to the production batches (refer to ICH Q5E). The analytical comparability for the clinical batches and the non-production batches to the production batches should be demonstrated. A comprehensive analytical comparability exercise may include additional characterisation testing.

4.1 Considerations for Selection of Primary Stability Batches

Where possible, batches of drug product included in stability testing should be derived from different batches of drug substance to account for variability in drug substance batches. Stability studies should be performed on each individual strength, fill volume and container closure system of the drug product unless a reduced protocol design is applied (refer to Annex 1 – Reduced Stability Protocol Design).

The primary stability batches of the drug substance and drug product should be representative of the clinical and production batches as described above. Additional development batches that are representative of the primary and production batches may also be included as supporting stability data.

Refer to Table 2 below for additional considerations at time of selection of primary stability batches.

Table 2: Considerations for Primary Stability Batches of Drug Substance and Drug Product

	Synthetic Chemical Entities	Biologicals
Drug Substance	• Same chemical synthetic route • Similar manufacturing process (differences justified) • At minimum, all batches manufactured at pilot scale[2] • Meet proposed registration specification • Containers constructed of the same material and type of container closure system as production batches.	• Same cell production system, if applicable • Similar manufacturing process (differences justified) • Meet proposed registration release specification • Containers constructed of the same material and type of container closure system as production batches. • Comparable to production batches (ICH Q5E)

Drug Product	• Same formulation[1] and dosage form • Minimum of 2 batches manufactured to at least pilot scale[2], other batch(es) can be smaller if justified • Same manufacturing process with equipment with the same operating principles. • Meet the proposed registration release specification • Same fill unless a reduced protocol design is applied[1] • Same container closure system as proposed for marketing	• Same formulation and dosage form • Comparable to production batches (e.g., ICH Q5E) • Meet proposed registration release specification • Same fill volume unless a reduced protocol design is applied[1] • Same container closure system as proposed for marketing.

[1]Refer to Annex 1 – Reduced Stability Protocol Design for details around when exceptions may apply

[2]In accordance with ICH Q13, the definition of a pilot batch for synthetics does not apply for continuous manufacturing.

When the long-term stability data do not cover the proposed re-test period or shelf life at the time the marketing application is submitted, refer to Section 15 - Stability Considerations for Commitments and Product Lifecycle Management for relevant commitments.

4.2 Considerations for Multiple Production Sites in the Initial Regulatory Submission

The stability data from each site, provided in the initial regulatory submission should be proportionate to the overall product, process and facility risk and in accordance with regional requirements. For both synthetics and biologicals, when the product, process and production site are comparable, the re-test period and/or shelf life would not need to be re-established at an additional production site. An additional production site refers to any production site proposed in the initial regulatory submission other than the drug substance and drug product site where the original production scale batches are manufactured.

For synthetic chemical entities, a comparison of batch data of the primary batches with data from each production site should be provided in the regulatory submission. The amount of stability data provided for each production site depends on the risk associated with implementing each additional production site for the drug substance or drug product. A commitment stability study should be established for each production site in accordance with Section 15.1 - Commitment Stability Studies. The number of production batches from each site in the commitment stability study can be fewer than three with a supporting scientific justification and risk assessment.

For biologicals, the default minimum stability data presented for each production site, should be as outlined in Table 1 of Section 3.2 -Recommended Minimum Core Stability Data for the Standard Approach at Submission to Support Initial Re-test Period or Shelf Life. However, for biologicals with an enhanced level of product and process understanding, an alternative science- and risk-based approach may be justified for those additional sites that are receiving the transferred manufacturing process from an originating production site. A comparability assessment inclusive of accelerated and/or stressed condition stability results for commercial scale production batches manufactured at the proposed additional site relative to primary batches from the original production site should be provided (refer to ICH Q5E). Based on risk assessment that considers analytical comparability, process comparability and production site history for the manufacture of similar product types, sites receiving the transferred manufacturing process may initially propose a reduced number of production scale stability studies in the regulatory submission. When a reduced data set is justified, a commitment should be made to continue stability studies at each site through the proposed re-test period or shelf life for a total of three production scale batches in accordance with Section 15.1 - Commitment Stability Studies.

4.3 Considerations for Vaccines

In general, production scale batches are expected to be used to set shelf life of vaccines. If non-production scale batches are used as primary batches, a justification should be based on product knowledge, comparability studies and risk. The remaining recommendations for primary batches for biologicals in Table 2 are also applicable to vaccines.

4.4 Considerations for Continuous Manufacturing Processes

For guidance on selection of batches from a CM process, refer to ICH Q13 guideline. For recombinant protein biologicals, the use of a single start-up/shutdown sequence (refer to ICH Q13) to manufacture multiple primary drug substance stability batches is typically not applicable. Primary drug substance stability batches should be obtained from multiple harvests/cell bank thaws and should cover the entire cell culture duration. The drug product primary stability batches manufactured by CM processes should incorporate the variability described for different drug substance batches.

5 CONTAINER CLOSURE SYSTEM

A container closure system comprises the primary (in contact with the product) and the secondary packaging if the latter are functional (e.g., combination of a drug product with a medical device) or intended to provide additional protection to the drug product. The stability study design should consider and include the secondary package when it is protective or directly impacts the chemical, physical, or functional attributes, unless otherwise justified.

The primary stability studies for the drug substance should be conducted in a container closure system that is the same or representative of the packaging proposed for storage and distribution. The container closure system should be the same type and constructed of the same material as production batches (dimensions may be smaller). For the drug product, the commercial container closure is recommended to ensure that the proposed container closure system can adequately protect the dosage form, is compatible with the dosage form and will function in the manner for which it is designed through a product's intended shelf life. When applicable, impact of packaging components from which matter may migrate into the product (e.g., ink or adhesive from labels) should also be considered.

Changes in the quality of a product may occur due to the interactions between the drug substance or drug product and the respective container closure system, and the effect of such interactions on product stability should be evaluated. Any impact of container orientation on the critical quality attributes of the drug product should be assessed based on prior knowledge gained through development and/or as part of stability studies. For primary batches of liquids, solutions, semi-solids and suspensions, the product should be placed into an inverted (or horizontal) position and an upright (or vertical) position unless a worst-case orientation is justified with supporting data. However, when drug product-container closure interactions cannot be excluded, stability studies should include samples maintained in both the inverted (or horizontal) position, as well as in the upright (or vertical) position (e.g., when storage orientation can have a significant effect on the delivered dose/repriming period of pressurised metered dose inhalers).

6 TESTING FREQUENCY

The proposed protocol should align with the principles outlined in Section 13 - Data Evaluation and include sufficient timepoints to verify any proposed extrapolation or stability model, where appropriate for the product type.

For primary stability studies, the frequency of testing should be sufficient to establish the stability profile of the drug substance or drug product. For a drug substance or drug product with a proposed re-test period/shelf life of 12 months or less, the frequency of testing at the long-term storage condition is recommended monthly for the first 3 months and at 3-month intervals thereafter. For cases when an intended re-test period/shelf life is very short, sufficient time points should be considered. For a drug substance or drug product with a proposed re-test period/shelf life greater than 12 months, the recommended frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year and annually thereafter through to the end of the proposed re-test period/shelf life. Sterility testing or alternatives (e.g., container closure

integrity testing) should be performed at a minimum annually, including initially and at the end of the proposed re-test period or shelf life.

For studies under accelerated conditions, a minimum of three time points, including the initial and final time points, is recommended (e.g., 0, 3 and 6 months is recommended for a 6-month study). Where an expectation (e.g., based on development experience) exists that results from accelerated studies are likely to approach significant change criteria (refer to Section 13 – Data Evaluation) or likely to be out of specification, increased testing is recommended. Increased testing could be conducted either by (a) including an additional less severe temperature condition (i.e., intermediate) that may be better predictive of the long-term stability and /or (b) including an additional time point in the accelerated study design which may be earlier than the final time point. Note that this would not preclude following the recommendations in Section 13 - Data Evaluation, when deciding whether extrapolation is applicable. At the intermediate storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9 and 12 months, from a 12-month study) is recommended.

As discussed in Annex 1 - Reduced Stability Protocol Design and Section 15.3 - Product Lifecycle Stability Studies, a reduced testing frequency may be justified when potential stability-indicating CQAs show no change over time. The minimum testing frequency recommended in this section may not be applicable if alternative strategies are applied (refer to Section 13 – Data Evaluation and Annex 2 – Stability Modelling).

7 STORAGE CONDITIONS

7.1 General Considerations

Stability of drug substances and drug products should be evaluated under storage conditions with appropriate tolerances that test for thermal and moisture stability and, if applicable, sensitivity to potential solvent loss. For sensitivity to light, refer to Section 8 – Photostability. The storage conditions and the duration of studies chosen should cover the intended storage and use, including considerations for shipment and any short-term storage condition (refer to Section 10 – Short-Term Storage Conditions). Advice on storage conditions to support an in-use period is detailed in Section 11 - In-Use Stability.

Testing at accelerated conditions or stress testing is essential to establish product stability information, such as to establish the degradation pathways and the intrinsic stability of the molecule, to confirm the stability-indicating nature of the analytical procedures (refer to Section 2 – Development Studies Under Stress and Forced Conditions and Section 3.3 – Stability-Indicating Critical Quality Attributes) and unintended excursions in storage conditions. Data generated under accelerated conditions may enable

stability modelling. Accelerated conditions data may support extrapolation of the intended re-test period and shelf life (refer to Section 13 – Data Evaluation).

Since most biologicals are sensitive to physical conditions, data obtained under accelerated conditions may confirm the stability-indicating nature of the analytical procedures or help elucidate the degradation profile of a biological drug substance or drug product. Data from accelerated conditions could also support that a manufacturing change did not impact the stability profile.

Where it can be justified that a proposed container closure system and conditions of storage afford sufficient protection against high and low humidity conditions, stability studies at different relative humidities can usually be omitted. Appropriate stability data under recommended storage conditions should be provided if containers other than impermeable containers are used.

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

Alternative storage conditions can be used if justified. Recommendations are applicable to both synthetic chemical entities and biological products, unless otherwise specified.

7.2 Considerations for Products Intended to be Stored at Room Temperature

The recommended storage conditions that are applicable to each climatic zone are outlined in the table below.

Table 3: Storage Condition Recommendations for Each Climatic Zone[1]

Climatic Zone[1]	Long-term[2]	Intermediate	Accelerated
I and II	25°C ± 2°C/60% RH ± 5% RH	30°C ± 2°C/65% RH ± 5% RH, or 30°C ± 2°C/75% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH
	30°C ± 2°C/65% RH ± 5% RH, or 30°C ± 2°C/75% RH ± 5% RH	Not applicable	40°C ± 2°C/75% RH ± 5% RH
III	30°C ± 2°C/35% RH ± 5% RH, or 30°C ± 2°C/65% RH ± 5% RH, or 30°C ± 2°C/75% RH ± 5% RH	Not applicable	40°C ± 2°C/75% RH ± 5% RH
IVa	30°C ± 2°C/65% RH ± 5% RH, or 30°C ± 2°C/75% RH ± 5% RH	Not applicable	40°C ± 2°C/75% RH ± 5% RH
IVb	30°C ± 2°C/75% RH ± 5% RH	Not applicable	40°C ± 2°C/75% RH ± 5% RH

[1]Specific regional requirements for more severe storage conditions may however apply

[2]Refer to Section 1.3 – Introduction to Guideline and General Principles

The applicant should determine and justify the long-term stability studies conditions to be performed.

In general, it is acceptable for stability information to be generated under a more severe climatic zone storage condition already defined in Table 3 to support the labelling. Testing at a more severe long-term condition (e.g., 30°C ± 2°C/75% RH ± 5% RH) could be justified as it encompasses all climate zones that a drug substance or drug product may be exposed to. However, if it is demonstrated that the drug substance or drug product will not remain within its acceptance criteria when stored at the more severe condition (e.g., 30°C ± 2°C/75% RH ± 5% RH) for the duration of the proposed re-test period or shelf life, the following are some approaches to consider:

- alternative long-term storage condition for the intended climatic zone.
- a minimal reduction in re-test period or shelf life.
- evaluation of stability in an alternative container closure system.
- evaluation of formulation and manufacturing process options.

When long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and a significant change occurs at any time during 6 months' testing under accelerated conditions, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria (refer to Section 13 – Data Evaluation).

If 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition defined.

For Climatic Zone III stability studies, an alternative approach to studying at the reference relative humidity (e.g., 35% RH ± 5% RH) can be achieved by performing the stability studies under higher relative humidity (e.g., 65% RH ± 5% or 75% RH ± 5%) through mathematical calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system (e.g., refer to Example 1 in Section 7.2.2 – Storage Conditions for Products Packaged in Semi-Permeable Containers).

7.2.1 Storage Conditions for Products Packaged in Impermeable Containers

Since drug substance and drug products packaged in impermeable containers (e.g., aluminium / aluminium foil blister, sealed glass container) provide a permanent barrier to passage of moisture or solvent, sensitivity to moisture or potential for solvent loss is not a concern. Thus, stability studies for products stored in impermeable containers can be conducted under any humidity condition.

7.2.2 Storage Conditions for Products Packaged in Semi-Permeable Containers

Sensitivity to moisture or potential for solvent loss is a concern for drug substance and drug products packaged in semi permeable containers. Semi-permeable containers can allow the passage of moisture, solvent, or gases while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material and desorption from the other surface. Transport across the container wall is driven by a partial pressure gradient.

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation should be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based products stored in semi-permeable containers can withstand low relative humidity environments.

For non-aqueous, solvent-based products, comparable approaches can be developed and applied.

654 **Table 4: Storage Condition Recommendations for Semi-Permeable Containers**

Long-term	Intermediate	Accelerated
25°C ± 2°C/40% RH ± 5% RH	30°C ± 2°C/35% RH ± 5% RH	40°C ± 2°C/not more than (NMT) 25% RH
30°C ± 2°C/35% RH ± 5% RH	Not applicable	

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656 Testing at a more severe long-term condition, e.g., 30°C ± 2°C/35% RH ± 5% RH could be justified.

657 A 5% loss in water from its initial value is considered a significant change for a product packaged in a
658 semi-permeable container after an equivalent of 3 months' storage at 40°C ± 2°C /NMT 25% RH.
659 However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an
660 equivalent of 3 months' storage at 40°C ± 2°C /NMT 25% RH may be acceptable, if justified.

661 A significant change in water loss alone under the accelerated condition does not necessitate testing at
662 the intermediate storage condition. However, data should be provided to demonstrate that no significant
663 water loss has been observed throughout the proposed re-test period / shelf life if stored at 25°C ± 2°C
664 / 40% RH ± 5% RH.

665 When long-term studies are conducted at 25°C ± 2°C/40% RH ± 5% RH, additional testing at the
666 intermediate storage condition should be performed to evaluate the temperature effect at 30°C if
667 significant change other than water loss occurs during the 6 months testing at the accelerated condition.

668 If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

669 An alternative approach to performing studies at the reference relative humidity as recommended in
670 Table 5 is performing the stability studies under higher relative humidity and deriving the water loss at
671 the reference relative humidity through calculation. This can be achieved by experimentally determining
672 the permeation coefficient for the container closure system (e.g., as shown in the illustrative example
673 below, using the calculated ratio of water loss rates for the container closure system between the two
674 relative humidity conditions at the same temperature). The permeation coefficient for a container
675 closure system can be experimentally determined by using the worst-case scenario (e.g., the most
676 diluted of a series of concentrations) for the proposed drug product.

677 *Example 1. An approach for determining water loss:*
678 For a product in a given container closure system, container size and fill, an appropriate approach for
679 deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured
680 at an alternative relative humidity at the same temperature by a water loss rate ratio determined

experimentally shown in Table 5 below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For the below illustrative example, at a given temperature (e.g., 40°C) the water loss rate determined experimentally for the proposed container closure system during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Table 5: Example of Ratio of Water Loss Calculations

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature[1]
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

[1]Ratio of water loss = (100 - Reference % RH)/(100 - Alternative % RH)

The ratios described in Table 5 above are for illustrative purposes. Actual ratios for water loss rates determined experimentally for the proposed container closure system under various relative humidity conditions should be provided.

7.3 Considerations for Refrigerated Temperature Storage

Recommendations for drug substance and drug products intended for long-term storage under refrigerated conditions are provided below. Accelerated conditions are intended to demonstrate the effect of temperature, and active humidity control may not be needed when justified.

Table 6: Storage Under Refrigerated Conditions

Long-term	Accelerated
5°C ± 3°C	25°C ± 2°C or any alternative temperature condition when justified.

For an aqueous-based product packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

For products stored under refrigerated conditions, when a significant change or out of specification occurs within the first 3 months of testing under accelerated conditions, a discussion should be provided to address the effect of shipment and handling (refer to Section 14 – Labelling).

For synthetics, it is considered unnecessary to continue to test a product under accelerated conditions through 6 months when a significant change has occurred within the first 3 months.

7.4 Considerations for Frozen Temperature Storage

Recommendations for drug substance and drug products intended for long-term storage under frozen conditions (as determined for the product) are provided below.

Table 7: Storage in a Freezer or below -20°C

Long-term
-20°C or below

Testing at accelerated or stress conditions (e.g., 5°C ± 3°C or 25°C ± 2°C or 30°C ± 2°C or any appropriate condition based on the intrinsic properties of the drug substance or drug product) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (refer to Section 14.1- Excursions Outside of a Labelling Claim).

8 PHOTOSTABILITY

8.1 Purpose of Photostability Testing

This section addresses the principles governing the generation of photostability information in initial regulatory submission and for lifecycle management changes.

The intrinsic photostability characteristics of a product should be evaluated to demonstrate that light exposure does not result in unacceptable change that could compromise product efficacy or patient safety. Normally, photostability testing is carried out on a single representative batch suitable for the purpose of the study. Repeating a photostability study may be required in response to relevant changes (e.g., in the formulation, container closure system and in-use conditions) when the photostability characteristics and controls established at the time of the initial regulatory submission are assessed to be impacted (refer to Section 15.3 – Product Lifecycle Stability Studies).

Two specific studies are performed to generate and evaluate photostability data:

- Forced photodegradation study – A study that may be an integral part of forced degradation evaluation and may be undertaken in the development phase. This information may be used to evaluate the overall photosensitivity of the drug substance and drug product for method development purposes, degradation pathway elucidation and to inform control strategies (refer to Section 2-Development Stability Studies Under Stress and Forced Conditions).

- Confirmatory photostability studies – Studies performed when a risk of photodegradation has been identified. The purpose of the studies is to establish the photostability characteristics to

understand the ability of the primary or secondary packaging material to protect light-sensitive products and the impact of light on product quality through manufacture, storage, transportation and in-use. These data may also support labelling (e.g., storage statements).

A systematic approach to photostability testing is recommended, covering as appropriate:

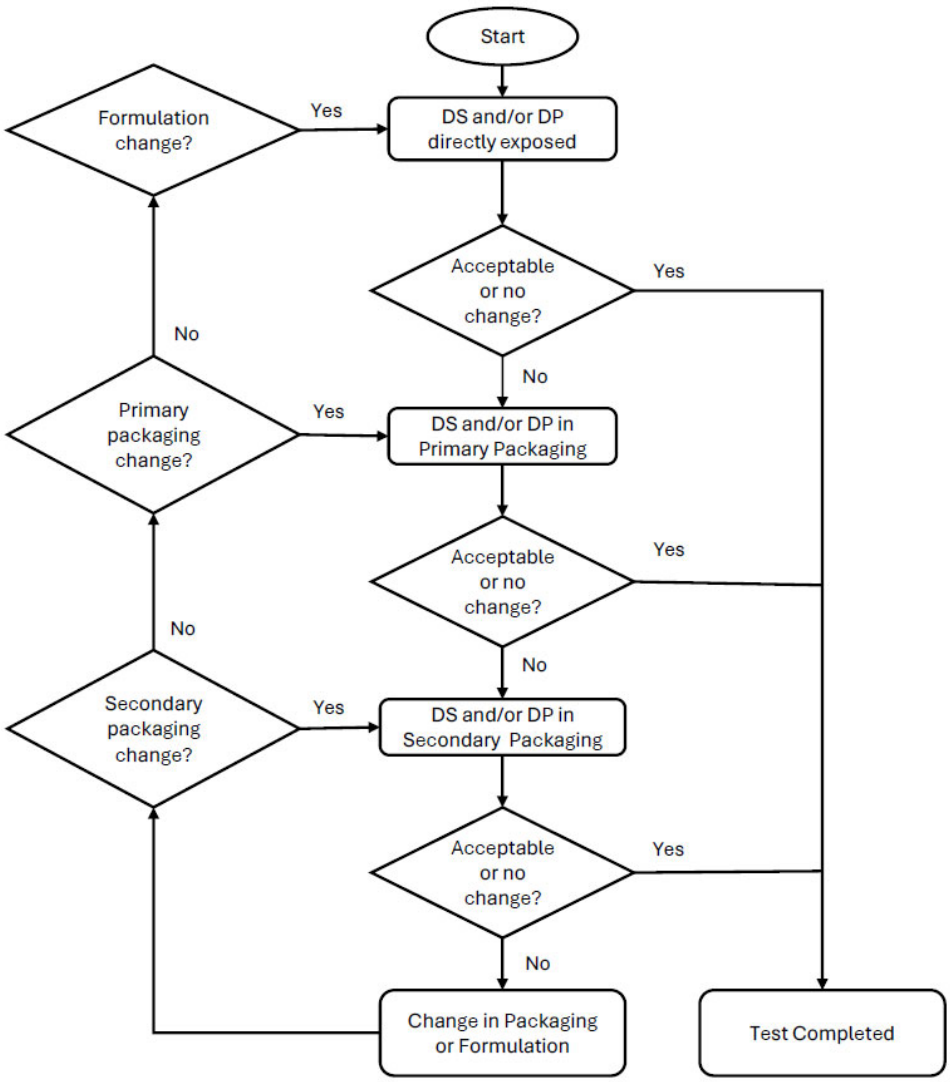
i) Tests on the drug substance and/or drug product directly exposed; and if necessary.

ii) Tests on the drug substance and/or drug product in the primary packaging; and if necessary.

iii) Tests on the drug substance and/or drug product in the secondary packaging.

Normally, the studies are carried out in a sequential manner starting with testing the sample directly exposed then progressing as necessary to the drug substance and/or drug product in the primary packaging and then in the secondary packaging, if applicable. If the product is known to be photosensitive, e.g., most biologicals, parallel testing can be carried out as a science- and risk -based approach. The extent of testing should be established by assessing whether acceptable change or no change has occurred at the end of the light exposure testing. Acceptable change is a change within limits previously justified by the applicant. If a non-acceptable change is observed, a change in the packaging or the formulation should be proposed. Testing should progress until the results demonstrate that the drug substance and/or drug product is adequately protected from exposure to light (refer to Figure 3 - Decision Flow Chart for Systematic Photostability Testing).

Figure 3: Decision Flow Chart for Systematic Photostability Testing



8.2 Forced Photodegradation

As forced photodegradation is an integral part of forced degradation strategy, details on the concepts, study design considerations and interpretation of results can be found in Section 2- Developmental Studies Under Stress and Forced Conditions. For details on radiation sources and light exposure conditions for forced photo degradation studies refer to Section 8.4 – Radiation Source and Light Exposure.

If the forced photodegradation study is combined with the confirmatory photostability study, the specific sample considerations provided in Section 8.3 - Confirmatory Photostability should be considered, e.g., for solid substances.

8.3 Confirmatory Photostability

The confirmatory studies are used to determine whether special precautionary measures are needed in manufacturing, formulation of the product, long-term storage or in-use period (refer to Section 11 - In-Use Stability) and if a light-resistant container closure system and/or special labelling information are needed. Guidance is provided on determining whether a confirmatory study should be performed, study design and interpretation of results (refer to Figure 3- Decision Flow Chart for Systematic Photostability Testing).

For synthetic chemical entities, confirmatory photostability testing is generally performed on one batch of the drug substance and the drug product, while for biologicals, testing is generally performed on one batch of the drug product. Confirmatory testing is typically conducted in the primary container closure system and including, if necessary, secondary packaging. Alternative science- and risk-based approaches may be considered when appropriately justified and may include scenarios where confirmatory photostability testing is not required. For example, if no photodegradation is observed in the fully exposed drug substance sample or the fully exposed drug product sample, no further testing as part of the confirmatory study is needed. For some products where it has been demonstrated that the primary packaging is completely impenetrable to light (e.g., aluminium tubes cans or foil/foil blisters) testing should normally only be conducted on directly exposed drug product.

If the results from the confirmatory study batch are not conclusive in terms of photostability or photolability, testing of additional batches or a new study design should be considered.

As a direct challenge for samples of solid products, an appropriate amount of sample should be taken and placed in a glass or plastic dish spread in a single layer and protected with a suitable transparent cover, if considered necessary. Tablets and capsules should be spread in a single layer. Solids, except tablets or capsules, should be spread across the dish to give a thickness of typically not more than 3 millimetres. When direct exposure is not feasible (e.g., liquids, or products sensitive to non-light induced oxidation), the sample should be placed in a suitable protective inert transparent container (e.g., quartz). In general, the samples should be positioned to provide maximum area of exposure to the light source.

If testing of the drug product in the primary or secondary packaging is needed, the samples should be placed horizontally or transversely with respect to the light source, providing the most uniform exposure of the samples. Some adjustment of testing conditions may have to be made when testing large-volume containers (e.g., dispensing packs). In general, samples with the greatest light exposure surface in the container should be tested.

At the end of the exposure period, representative samples (taking homogeneity of light exposure into consideration) should be examined by analytical procedures (suitable for intended purpose) for any changes in physical, chemical or biological properties, including assay or potency and degradants that are determined from the characterisation studies that are likely to arise from photochemical degradation. When powder samples are involved, sampling should ensure that a representative portion is used in individual tests. For solid oral dosage form products (e.g., tablets, capsules), testing should be conducted on a suitable number of units (statistical sampling approaches may be used). Similar sampling considerations, such as homogeneity or solubilisation of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions).

The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies to assure that the product will be within proposed specifications during the re-test period or shelf life. Depending on the extent of change or failure to meet acceptance criteria, special precautions may be needed to mitigate exposure to light, like formulation change, redesign of container closure system (including secondary packaging), a reduced re-test period or shelf life of drug substance or drug product (in conjunction with long term stability data) or change in labelling for storage and use (refer to Figure 3 - Decision Flow Chart for Systematic Photostability Testing).

8.4 Radiation Source and Light Exposure

This section describes the radiation source and light exposure that can be used to support forced photodegradation studies and confirmatory photostability studies. For forced degradation studies a variety of exposure conditions may be used, depending on the photosensitivity of the product and the intensity of the light sources used. Confirmatory photostability studies should be based on light exposure possible during manufacture, storage, distribution and in-use.

In photostability studies, it is important to consider the spectral characteristics of the light, cumulative light exposure and temperature, as the combination of these factors will influence the rate of photodegradation and the design of the study.

The light sources described below are considered appropriate for photostability testing. Alternative light sources may be applicable when justified. The applicant should either maintain appropriate temperature control to minimise the effect of localised temperature changes or include a dark control in the same environment unless otherwise justified. The applicant may rely on the spectral distribution specification of the light source manufacturer for the following options:

Option 1:

For light exposure similar to the D65 (outdoor daylight) emission standard (as currently defined in, ISO/CIE 18909:2022) (17), an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon or metal halide lamp, including appropriate filter(s) is recommended as radiation light source.

Option 2:

A combined exposure to both cool white fluorescent and near ultraviolet lamp, which is capable of producing a light exposure similar to the ID65 (indoor daylight) emission standard, for which the ultraviolet lamp has at least 25% of the ultraviolet-A between 320 and 360 nm and at least 25% is between 360 and 400 nm.

Option 3:

Ambient/mild light conditions (predominantly light >400 nm during manufacturing, processing and in-use), for which a fluorescent or LED lamp is recommended.

Light exposure for forced photodegradation studies may require higher light intensity, such as doubling the levels used in confirmatory studies. However, depending on the photosensitivity of the product, milder conditions may be more suitable to avoid extensive decomposition. For example, samples might be exposed to ambient/mild light conditions, typically ranging from 43-260 $\times 10^3$ lux hours for >400 nm and 0.3-3 Wh/m^2 for 350 – 400 nm, over an exposure period of 1 to 7 days.

In confirmatory studies, to assess the effects of light under controlled conditions during manufacturing, storage and in use, samples maybe exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 Wh/m^2. When justified, alternate approaches may also be appropriate depending on the photosensitivity of the product, the light source selected, manufacturing conditions and packaging. The overall light exposure during manufacture can be determined by measuring the light exposure and defining the average light exposure and UV energy (e.g., in Luxh and/or Wh/m^2). The average light exposure reading, with the worst-case light exposure time, could be used to define light exposure time and distance to light source considerations in the confirmatory study.

9 STABILITY CONSIDERATIONS FOR PROCESSING AND HOLDING TIMES FOR INTERMEDIATES

9.1 General Considerations

Good manufacturing practices (GMP) and good distribution practices (GDP) require that controls are in place to ensure that intermediates (i.e., drug substance intermediates and drug product intermediates (including bulk drug products)) are manufactured and stored under appropriate conditions. Storage and/or transportation arrangements should not have deleterious effects on the subsequent processing, stability, safety, or quality of intermediates, in accordance with good distribution practices.

The processing time can be considered as the established time period needed to perform a manufacturing step or series of steps and should take into consideration compatibility with manufacturing equipment. Whereas the holding time can be considered as the established time period for which materials (e.g., dispensed raw materials, drug substance intermediates and drug product intermediates) are awaiting further processing or packaging in the final container closure system and may be held and/or transported under specified conditions. For such intermediates, maximum holding times should be established to ensure their quality and that they can be held, pending the next processing step, without having results outside the established control strategy. Intermediates should not be used beyond the established holding times. A written protocol, procedure or program for the holding time studies should be followed taking into consideration the principles described in Section 3.1 – General Principles.

The data used to establish the holding time should cover the proposed holding times for the intermediates and the stability studies should be performed at relevant temperature and humidity conditions to support the expected storage conditions for the drug substance or drug product intermediate. If the temperature and humidity conditions used during these studies do not correspond with the storage conditions described in Section 7 - Storage Conditions of this guideline, other conditions should be justified. If the product is sensitive to light exposure that may occur during storage, data should confirm that controls are sufficient to limit exposure to acceptable levels as described in Section 8 - Photostability. If more than one production site is involved, the stability studies should also consider transportation of the intermediates. For consideration of reduced design, the principles of Annex 1 - Reduced Stability Protocol Design may apply. Cumulative hold times are generally assessed as part of process validation. If a stability risk is identified, a cumulative holding time study may be necessary.

For drug substance and drug product intermediates that are packaged and stored outside of the manufacturing process activities or that are purchased as such, it may be appropriate to establish a re-test period or shelf life, as applicable, rather than a holding time. In these situations, the

recommendations described in the respective sections within this guideline should be followed for the stability studies conducted to support the re-test period or shelf life with the corresponding storage statements.

Stability recommendations for intermediates, including considerations that are specific for synthetic chemical entities and biologicals, are described below.

9.2 Considerations for Synthetic Chemical Entities

The holding times of the drug substance intermediates should consider GMP principles and comply with written procedures. However, in situations where an in-process step for the drug substance has a holding time where the quality of the drug substance may be affected by the hold, then the principles in this section apply.

When established, the processing times and maximum holding times for drug product intermediates should be included in the description of the manufacturing processes. The risk assessment and control strategy for the drug product manufacturing processes should include an assessment of whether holding time studies should be performed. When applicable, the information to support the processing and holding times should be included in the regulatory submission.

When the holding times of a drug product intermediate are prolonged (e.g., more than 30 days for solid dosage forms for the entire manufacturing process or more than 24 hours for non-solid dosage forms or sterile products), evidence of the suitability of the holding times, together with the proposed container that is representative of that for marketing, the storage period or transportation arrangements, should be included in the regulatory submission, when requested. Where intermediates are transported between production sites, the transportation arrangements and method of transportation should be described in general terms (e.g., intermediate container, storage and transportation conditions) in the description of the manufacturing processes.

For a drug substance or drug product produced by batch processes (i.e., not by continuous manufacturing processes), it is expected that the data to support the holding times is generated and is representative of the overall process. If the data to support the holding times were not generated on production scale batches, these data should be verified in post-approval stability commitment to conduct these studies on production scale batches. If continuous manufacturing processes are used, the principles outlined in ICH Q13 guideline should be followed when selecting batches to support holding times.

9.3 Considerations for Biologicals

During the manufacture of biologicals, the quality and control of certain process intermediates may be critical to the production of the drug substance or drug product. In general, the manufacturer should

identify process intermediates and generate data and define process limits and holding times that assure their stability within the conditions of the developed manufacturing process. Samples are periodically tested for product quality attributes that may be affected by the holding time.

A holding time study for a biological will typically consider two elements: (a) physicochemical stability and (b) microbial control strategy. The physicochemical stability part may be performed on small scale batches that are representative of production scale as part of process characterisation and should be assessed by monitoring relevant CQAs, such as purity and impurity. Microbial control should be demonstrated for the manufacturing process of production scale batches. The use of surrogate material as well as other approaches should be justified.

When physicochemical and microbial hold times are determined from separate studies, the established hold time would be the shorter of the two times.

When analytical procedures cannot be applied to an intermediate to determine its holding time, the adequacy of the holding time could be supported by evaluating the quality of the later stage intermediates, drug substance, or drug product.

9.4 Examples of Holding Time Risk Assessment Considerations

The following are examples of the stages that may be considered during the risk assessment of two different types of drug product manufacturing process. Depending on the dosage form, other stages and considerations could be relevant.

9.4.1 Non-Sterile, Solid Oral Dosage Form

The following are examples of the stages that may be considered during the risk assessment of the drug product manufacturing processes for a for a non-sterile, solid oral dosage form to identify potential processing and holding times for intermediates. Depending on the dosage form, other stages and considerations could be relevant.

Table 8: Production steps and associated intermediates for non-sterile, solid oral dosage form

Production Step	Intermediate
Binder preparation to granulation	Granulate
Wet granulation to drying	Dried granulate
Dried granules to lubrication/blending	Lubricated blend
Mixing to a dry blend	Blend
Granulation to compressed tablets	Tablet Cores
Coating solution/suspension to preparation	Coating solution/suspension

Coating to packaging in bulk containers	Bulk coated tablets

941

942 **9.4.2 Sterile, Injectable Solution**

943 The following are examples of the stages that may be considered during the risk assessment of the
944 manufacturing processes for a sterile, injectable solution to identify potential processing and holding
945 times for intermediates:

946 • Processing times at 15-25°C during drug substance process to bulk drug substance
947 • Frozen in-process materials
948 • Processing time at room temperature (e.g., 15-25°C) from start of drug product manufacturing
949 (e.g., drug substance thaw) until end of fill

950 ## 10 SHORT-TERM STORAGE CONDITIONS

951 The drug product labelling (refer to Section 14 – Labelling) may specify a short-term storage condition
952 for a drug product. Short term storage is a condition where the primary container closure is not breached
953 and that is different form the long-term storage condition and the in-use period. The short-term storage
954 condition does not need to be implemented by the patient/health care professional, as use of short-term
955 storage is optional. The short-term storage condition is intended for convenience of the patient or health
956 care professional in accordance with regional requirements based on anticipated storage of the drug
957 product. For example, a short-term storage condition would enable a patient to store a refrigerated drug
958 product at a room temperature condition for a specified duration of time. In these cases, the short-term
959 storage condition and duration should be stated on the labelling along with the long-term storage
960 condition and shelf life. The short-term storage condition is not intended to be applied beyond the shelf
961 life of the drug product. The short-term storage condition is different from any necessary manipulation
962 (e.g., equilibration to ambient temperature) that would be required to prepare a drug for administration
963 (e.g., as per relevant instructions in Instructions for Use). If the drug product can be returned to long-
964 term storage conditions after an acceptable period of short-term storage, data to support the short-term
965 storage conditions should be provided as part of the primary stability studies. A short-term storage
966 condition is not required for all products. Once a short-term storage condition is established it does not
967 need to be reevaluated periodically unless there is a change likely to impact stability.

968 The design of specific short-term storage condition stability studies should follow the general principles
969 applied to long-term stability studies (refer to Section 3 – Stability Protocol Design) and should consider
970 all relevant climatic zones. Generally, a minimum of 2 batches should be included in the study. The
971 number of batches and the considerations for aged sample should be based on the general principles

described for in-use stability studies (refer to Section 11.2.1 – Selection of Batches). Additionally, the applicant may justify alternative strategies, such as modelling (refer to Annex 2 – Stability Modelling), to support the short-term storage condition.

The applicant should demonstrate that drug product with a proposed short-term storage condition will remain within the shelf life specifications.

11 IN-USE STABILITY

11.1 Purpose of In-Use Stability Testing

This section describes the principles for in-use stability testing for the purpose of establishing or confirming an in-use period and storage conditions, during which the quality of the drug product is maintained within the pre-defined acceptance criteria. In-use conditions are defined as the conditions that mimic the intended use of the drug product after the primary container is first breached and, where applicable, through preparation, storage and administration as per the relevant instructions. The principles outlined in this section are generally applied to single-dose drug products that are handled or prepared and stored prior to administration, including dilution, reconstitution or co-mixing, as well as single containers or combinations of a drug product with a medical device containing drug product intended for multiple administrations or doses. Products packaged in single-use containers for immediate use and not requiring preparation generally do not require an in-use period and would not be subject to in-use stability testing. Assembly of a combination of a drug product with a medical device for immediate use does not constitute preparation in the context of in-use stability testing.

For a drug product that may remain in contact with a delivery device during administration over time under conditions that differ from the proposed storage (e.g., implantable infusion pump containing the drug product), an in-use study should demonstrate that the drug product remains stable and does not negatively impact the device delivering the drug during the in-use duration.

The conditions of use for those products requiring preparation and for multi-dose products may pose a risk to quality of the drug product regarding physicochemical properties and/or microbiological contamination. The regulatory submission for these products should include in-use stability data, upon which the in-use period and instructions are based. This section defines a core framework for establishing or confirming an in-use period and storage conditions, including selection of batches, study design, analytical procedures and acceptance criteria, that are applicable across multiple product types. It is expected that the material in contact with the product and used in the preparation and administration should be demonstrated to be compatible for use with the drug product.

Under some circumstances these studies may need to be repeated if certain post-approval variations and changes are made to the product (e.g., formulation, container closure system). To determine whether these studies should be repeated, an assessment of change should be performed according to Section 15.2 - Risk Assessments and Confirmatory Studies to Support Post-Approval Changes.

11.2 In-Use Stability Study Protocol Design

The design of in-use stability study protocols should follow the general principles outlined in Section 3 - Stability Protocol Design. The protocol should simulate the intended use of the product, as detailed in the relevant instructions (e.g., for a multi-dose product stored in a vial, the in-use studies should demonstrate that the container closure system can withstand the conditions of repeated insertion and withdrawal). When designing in-use studies, conditions under which a drug product could be used, including the maximum time the drug product will be exposed to different environmental factors during use, should be considered. For samples requiring preparation, including reconstitution, dilution, or co-mixing, the in-use studies should demonstrate the stability of the product through preparation and handling under the specified storage conditions for the maximum storage period. The study duration, conditions and selection of the analytical procedures and acceptance criteria should be justified as suitable for demonstrating that product quality is maintained throughout the in-use period. Storage conditions and withdrawal frequency should, at minimum, reflect the instructions-for-use or may consider a worst-case scenario.

Alternative (e.g., worst-case) approaches to protocol design may be considered when appropriately justified. For example, for solid oral doses, the applicant may justify the use of open dish studies instead of an in-use study.

11.2.1 Selection of Batches

Generally, in-use stability data should be provided on two batches of representative drug product. Based on a risk assessment considering product knowledge and available primary stability data, alternative approaches to batch selection may be considered when appropriately justified. At least one of the batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies. If aged batch data are not available at time of filing, a commitment to provide the data or a justification why those data may not be required based on a risk assessment should be provided in the regulatory submission.

All in-use stability batches should be provided in the container closure system proposed for commercial use (e.g., multi-dose vial, assembled multi-dose combination of a drug product with a medical device), or the administration set up. For drug products presented with different fill volumes, strengths, or

presentations, a representative, worst-case or, bracketing or matrixing approach may be applied with justification (refer to Annex 1 – Reduced Stability Protocol Design).

11.2.2 Selection of Analytical Procedures and Acceptance Criteria

The analytical procedures with acceptance criteria included in the study should be justified using a risk-based approach that considers the CQAs most likely to change during the proposed in-use period (refer to Section 3.3 - Stability-Indicating Critical Quality Attributes). The analytical procedures should be suitable for the intended purpose and selected to demonstrate the physical, chemical and microbial stability of the product through the proposed in-use period.

For synthetic chemical entities, the physical and chemical quality attributes selected should be appropriate to the individual dosage form and formulation. For example, attributes such as colour, odour, clarity, closure integrity, particulate matter, particle size, moisture content, drug substance assay(s), degradation product level(s), dissolution, antimicrobial preservative and antioxidant content(s), pH and viscosity, and microbial testing should be considered for testing, as applicable with additional considerations for risk associated with dosage form.

For biologicals, the physical and chemical quality attributes selected should be appropriate to the individual dosage forms (18). For example, physical and chemical quality attributes of protein content, appearance, clarity, colour, visible particles and high molecular weight species should be tested, unless otherwise justified, while product-related variants or impurities and sub-visible particles should be tested where applicable. Potency testing, or an analytical procedure covering the mode of action, should be included where applicable and potential analytical limitations should be understood. Microbial stability should be assessed through the proposed in-use period for biologicals. Common recommended testing includes a Preservative Efficacy Test (PET) / or Antimicrobial Effectiveness Test (AET), or a microbial enumeration method (e.g., bioburden). In lower risk situations, it may be possible to justify the absence of microbial testing where appropriately justified and based on an assessment of risk.

11.3 Labelling of the in-use period and storage conditions

In-use stability data should be used to determine whether a declaration of an in-use period and storage condition are necessary. The in-use period and storage conditions should be stated on the labelling in accordance with regional regulations.

There may be scenarios where an established in-use period may not be needed in the labelling. For example, prepared orally administered products, stored in multi-dose containers with a defined supply that is intended for continuous use (not intermittent dosing), may not need to include an in-use period on the labelling if the demonstrated in-use stability data support storage for the intended use of the product.

12 REFERENCE MATERIALS, NOVEL EXCIPIENTS AND ADJUVANTS

This section covers stability considerations for reference materials, novel excipients (e.g., those used for the first time in a drug product or through a new route of administration) and adjuvants. Novel excipients and adjuvants are discussed due to their significant potential impact on the quality of the drug product.

Additives (e.g., stabilisers and preservatives) may degrade during the re-test period or shelf life of the drug substance or the shelf life of the drug product. These materials (additives) should be monitored during the stability program if there is an indication that their reaction, degradation, or depletion will adversely affect the quality of the drug product. Refer to Section 3.3 Stability-Indicating Critical Quality Attributes for general stability study design considerations.

12.1 Reference Materials

Reference materials (as defined in ICH Q2/Q14), that are used to control the quality attributes of a stored intermediate, drug substance, or drug product should be sufficiently homogenous and stable to ensure scientifically valid results are achieved. If the formulation, material composition, storage condition and/or container closure system for the reference material is different from the drug substance or drug product, a specific reference material stability program may be needed, with an established use period that reflects the differences. Externally sourced, well-characterised reference materials should follow manufacturer recommendations for stability and storage and should be managed within the quality management system (e.g., pharmacopeial materials). Stability data should be available to support the use period of the in-house reference material. These data are generally provided with the regulatory submission for biologicals and managed within the pharmaceutical quality system (PQS) for synthetics.

12.1.1 Considerations for Synthetic Chemical Reference Materials

The use period of a synthetic chemical drug substance, intermediate and drug product reference material may be extended through acceptable stability data and requalification according to established control strategy under a PQS. A synthetic reference material may be stored under more conservative storage conditions than the drug substance and drug product.

12.1.2 Considerations for Biological Reference Materials

The use period of a biological reference material, when kept under conditions used to store the corresponding drug substance, intermediate or drug product, should generally be supported by available long-term stability data. When a well-characterised drug substance or drug product is used as an in-house reference material and the storage conditions are the same as that used to store the drug substance

or drug product, the drug substance or drug product stability data may support the reference material use period, without a need for additional reference material specific stability testing.

Alternative storage conditions may extend the use period of in-house biological reference materials beyond the re-test period or shelf life of the drug substance, intermediate, or drug product (e.g., stabilising storage at a sufficiently lower temperature than the drug substance or drug product storage condition). The alternative storage condition should be justified with its own long-term stability data or a concurrent stability testing strategy that allows for a trend analysis of the data. The reference material use period may be extended through acceptable stability data according to a protocol (e.g., qualification).

In situations where a drug substance or product's stability-indicating critical quality attribute (e.g., potency) is being controlled relative to a reference material, a risk-based approach, including more stringent stability acceptance criteria and trend analyses, should be considered for the reference material's stability to prevent drift in the stability profile of the drug substance or product.

12.2 Novel Excipients

Novel excipients should be evaluated for their impact on the stability of the drug product and relevant information should be included in the regulatory submission following the recommendations described in the applicable sections within this guideline (refer to Section 3 - Stability Protocol Design, Section 6 -Testing Frequency and Section 7 - Storage Conditions). If the excipient itself is a protein (e.g., albumin) and used with a biological drug substance, additional risk assessments should be provided to clarify the known degradation profile of the excipient and its impact on the biological drug substance or drug product. For protein-based excipients, the drug product stability studies should address their potential protein-excipient interaction, quantity of intact excipient in the drug product and impact on drug product immunogenicity as well as their potential for masking process related impurities.

12.3 Vaccine Adjuvants

Adjuvant stability data should be provided in the regulatory submissions for vaccines. Stability of the adjuvant should be assessed by formal stability studies. If alternative strategies for determining stability of the adjuvant are potentially applicable, the applicant should consider early engagement with the regulatory authority.

The stability studies will depend on the formulation/presentation, where vaccine drug product formulated with the adjuvant will have different consideration to formulations where the adjuvant is provided in a separate vial to the vaccine drug product. For adjuvants that are mixed with the drug substance at the production site to derive the adjuvanted vaccine drug product, data that support shelf life of the adjuvanted vaccine in the primary container is required. In case of adjuvanted vaccines that

depend on antigen adsorption to the adjuvant (e.g., alum/antigen mixture) stability monitoring should consider the degree of antigen adsorption/binding and extent of dissociation of antigen from the adjuvant upon storage, where relevant.

When the adjuvant and vaccine antigen (vaccine components) are supplied in separate containers, the stability of each component should be assessed following appropriate pre-defined protocols that reflect storage duration and storage conditions of each vaccine component.

The in-use stability of the adjuvant-antigen mixture should be assessed in the situation when the mixture is not administered immediately after preparation and should be performed at the intended in-use conditions and period (refer to Section 11 – In-Use Stability). It is important to set appropriate acceptance criteria to assess integrity of the adjuvant in the adjuvant/vaccine antigen mixture. The data generated in the in-use stability studies will support the instructions for use of the admixed vaccine.

13 DATA EVALUATION

13.1 General Considerations

Stability data are obtained for multiple purposes throughout the product lifecycle. A systematic approach should be adopted in the presentation and evaluation of the stability information. This section focuses on the evaluation of stability data to establish a re-test period or shelf life for drug substance and the shelf life for drug product based on long-term data at the recommended storage condition. Refer to Section 3 - Stability Protocol Design, Table 1 for the minimum stability data at the time of submission. Alternatively, when there is limited long-term stability data at the recommended storage condition, the re-test period or shelf life can be proposed based on:

- Use of enhanced stability modelling methodologies to predict or extrapolate the stability profile past the point of the available real-time data (refer to Annex 2 – Section A2-2- Enhanced Stability Modelling).
- Limited extrapolation of the real-time data for synthetic chemical entities that may be supported by accelerated condition stability data using a decision tree approach. For biologicals, the decision tree approach, which is based on the extent of attribute change at accelerated storage conditions, is not considered suitable due to the inherent differences in degradation mechanisms and other structure/function differences within biologicals.

A comprehensive stability data evaluation should take into consideration any stored intermediates, process hold times, any short-term storage outside of the long-term storage conditions, including the risk of excursions to the storage conditions and manipulations of the product to the completion of administration to the patient (in-use stability).

Guidance is provided for the data evaluation of drug substance and drug product that have stability data from at least three primary batches with batch as a single factor, and multi-factor products with full design (for example, products with the same drug substance at different fill volumes, varied concentration, container closure system dimensions, etc.). In addition, the degree of variability between batches and other factors affect the confidence that a future production batch will remain within acceptance criteria throughout its re-test period or shelf life. Multi-factor products with reduced design studies are discussed in Annex 1 - Reduced Stability Protocol Design.

When the principles for extrapolation and modelling are considered to apply to other product types, such as ATMPs or vaccines**,** the applicant should seek early engagement with the regulatory authority.

13.1.1 Re-Test Period

A re-test period is normally applicable to drug substances of synthetic chemical entities as an alternative to establishing a shelf life. This approach may also be proposed in certain cases for the drug substances of biologicals with a well understood stability profile, where justified. An example where a re-test period may apply for a biological drug substance is a well characterised IgG therapeutic monoclonal antibody that is stored frozen and shows little to no change in product quality over the duration of storage.

13.1.2 Start of Shelf Life for Synthetic Chemical Entity Drug Products

The start of shelf life should be the date of production, which is defined as the date of the first manufacturing step that combines drug substance with other ingredients.

In accordance with regional requirements, consider the following approaches:

- When the date of release is less than 30 days from the date of production, the start of shelf life of a drug product batch could instead be calculated from the date of release of that batch.
- For drug products consisting of a drug substance as a single ingredient, filled into the final drug product container, the initial date of the filling operation is taken as the date of production.

In the case of a drug product intermediate storage step before further processing and when the start of shelf life is not defined as described above, these should be declared and justified and included in the drug product stability program of batches that represent the cumulative maximum holding times of drug product intermediates.

13.1.3 Start of Shelf Life for Biological Drug Products

The start of shelf life for biological drug products begin on the date of manufacture e.g., date of filtration and/or filling for a liquid drug product. When the drug product filling operation takes place over more

than one day, then the initial date of the filling operation is taken as the date of manufacture. Other approaches used to define the start of shelf life can be used if justified.

13.2 Statistical Evaluation of the Long-term Storage Condition Stability Profile to Establish the Re-test Period or Shelf Life

All stability data from the primary and supportive stability studies should be evaluated to establish a re-test period or shelf life. The statistical evaluation should include all primary stability studies, any available production scale studies and supplemented, when applicable, with additional supportive data from batches included in the stability programme (refer to Section 4 - Selection of Batches). The stability profiles for the CQAs shown to potentially change over time at the recommended storage conditions should be evaluated to establish the re-test period or shelf life. Each CQA should be assessed separately, and an overall assessment should be made of findings for the purposes of proposing a shelf life or re-test period. The re-test period or shelf life proposed should not exceed that predicted for any single attribute.

Data from quantitative analytical procedures should be evaluated using appropriate statistical tools; whereas results from semi-quantitative or qualitative analytical procedures, which may not be amenable to statistical analysis, should also be evaluated. The degree of variability across individual batches and the number of data time-points affects the confidence that a future production batch will remain within specification throughout the established re-test period or shelf life (24).

There are many valid statistical methods to evaluate stability data to set a re-test period or shelf life from batches of substances, intermediates, or products. The statistical methodology used should be justified as suitable for the product type, the data set used for the analysis (batches, study design factors, etc.) and the purpose of the evaluation. The following sections outline selected, commonly used approaches and do not cover all situations (26, 27).

13.2.1 Linear Regression for an Individual Batch

Each primary batch, stored under the long-term conditions, may be evaluated individually to establish the re-test period or shelf life. Where there are differences in stability observed among batches or among other factors or factor combinations that preclude the combining of data, the proposed re-test period or shelf life should not exceed the earliest time (worst-case) period supported by any batch, other factor, or factor combination. For quantitative attributes expected to change with time following a linear pattern or log transformed data that follow a linear pattern at the recommended storage condition, an approach for evaluating the data is by linear regression analysis. The appropriateness of the assumed linear relationship over time and normal distribution of the variables may be supported by evaluation of the residuals for the regression line (goodness of fit).

Analyses of a quantitative attribute can be performed by determining the earliest time at which the 95% percent confidence limit for the mean intersects the proposed acceptance criterion. For attributes with upper and lower acceptance criteria, a two-sided 95% confidence limit is recommended. The point at which the confidence limits for the mean intersects the acceptance limit for each individual batch under evaluation is generally determined (illustrated in Annex-2 Stability Modelling for an individual batch example). Using this approach, the upper and lower limits may each be evaluated individually as one-sided limits against their respective upper and lower acceptance criteria. For attributes with only a lower or an upper acceptance criterion, such as those for purity/impurity, a one-sided 95% confidence limit is recommended.

Re-test period or shelf life for individual batches should first be estimated with individual intercepts, individual slopes and the pooled mean square error calculated from all batches. If each batch has an estimated re-test period or shelf life longer than that proposed, the proposed re-test period or shelf life will generally be considered appropriate. If, however, one or more of the estimated re-test periods or shelf lives are shorter than that proposed, a statistical test can be performed to determine whether the batches can be combined to estimate a longer re-test period or shelf life.

13.2.2 Combining Batches

For the statistical evaluation, it may be advantageous to combine the data from different representative batches into one overall estimate. A linear regression analysis provides a test for the parameters that define the linear stability profile of an attribute from a single batch and whether they can be combined to determine: first the change over time or slope followed by the y-intercept. An appropriate statistical approach should be prospectively defined and justified to evaluate the ability of combining data from different batches (22, 23). Refer to Annex 2 - Stability Modelling for additional statistical considerations. A simulation study can be useful, if applicable, to demonstrate that the statistical properties of the procedure selected are appropriate (25).

13.2.3 Scale Transformation of Data

When the degradation kinetics are complex and decelerating (e.g., a biphasic degradation profile characterised by fast initial rate followed by a slower longer-term rate or when the data that may show a plateauing profile), a linear regression analysis could be proposed when the linear regression provides a worst-case shelf life or re-test period. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. The relationship can be represented by a linear or non-linear function on an arithmetic or logarithmic scale. In some cases, a non-linear regression can better reflect the true relationship. It should be noted that in some instances if a linear function is fit to plateauing data, data points beyond the plateau could skew the regression line towards later timepoints. Whereas this section describes linear regression analysis, other approaches

may be used (e.g., nonlinear regression) with justification. When scale of transformation is used, statistical methods should be prospectively employed to evaluate the goodness of fit on all batches and combined batches (where appropriate) to the inferred degradation profile. Transformation of a non-linear model should be justified from a scientific perspective (e.g., understanding of the attribute and/or analytical procedure).

13.2.4 Extrapolation and Stability Modelling

Extrapolation is the practice of using a known data set to infer information about future data and is a form of stability modelling that, under certain conditions, may be applicable to synthetics and biologicals. Extension of shelf life beyond the period covered by long-term data, by extrapolation, can be proposed in the regulatory submission. Whether extrapolation of stability data is appropriate depends on the extent of understanding for the product type, relevant knowledge about the stability-indicating attributes and any change over time, the goodness of fit of any mathematical or other computational model type, and the existence of relevant supporting data that may include additional timepoints, additional batches or prior knowledge. Relevant supporting data include satisfactory long-term data from development batches that are (1) made with a comparable formulation to, (2) manufactured on a smaller scale than, or (3) packaged in a container closure system similar to that of the primary stability batches.

For synthetics, certain quantitative chemical attributes (e.g., assay, chemical degradation products, preservative content) for a drug substance or product can generally be assumed to follow zero-order kinetics during long-term storage. Although the kinetics of other quantitative attributes (e.g., pH, dissolution) are generally not known, the same statistical analysis can be applied, if appropriate. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis. The decision tree approach would not be recommended for biological products because biological and immunological attributes are generally not amenable to extrapolation, as they cannot be assumed to follow zero order kinetics. For certain well characterised biologicals that have no statistically significant or meaningful change over time, extrapolation may be possible using the risk assessment criteria and supporting long term development data, as outlined in Section 13.2.9 – Extrapolation of Biologicals.

An extrapolation of stability data assumes that the same change profile will continue to apply beyond the period covered by available long-term data and should be applicable to future batches. The correctness of the assumed change profile is a critical consideration, especially when stability data are limited. Any extrapolation should be justified and have a science-based rationale that may be based on prior knowledge.

The methodologies outlined in this section may be used to extrapolate the long-term stability data. When estimating a regression line or curve to fit the long-term data, the data themselves provide a check

on the correctness of the assumed change pattern, and statistical methods should be applied to evaluate the goodness of fit (or an equivalent valid statistical method) of the existing data to the inferred line or curve and to provide confidence that future batches will lie within the inferred stability profile (refer to Annex 2, Section A2-1 - Statistical Evaluation of Stability Data from Single or Multi-factor Study Designs). No such internal check is possible beyond the period covered by long-term data from primary batches, though an inferred trend may be supported by prior knowledge.

Enhanced stability modelling, such as those referenced in Annex 2 (Annex 2- Section A2-2 Enhanced Stability Modelling) may also be considered.

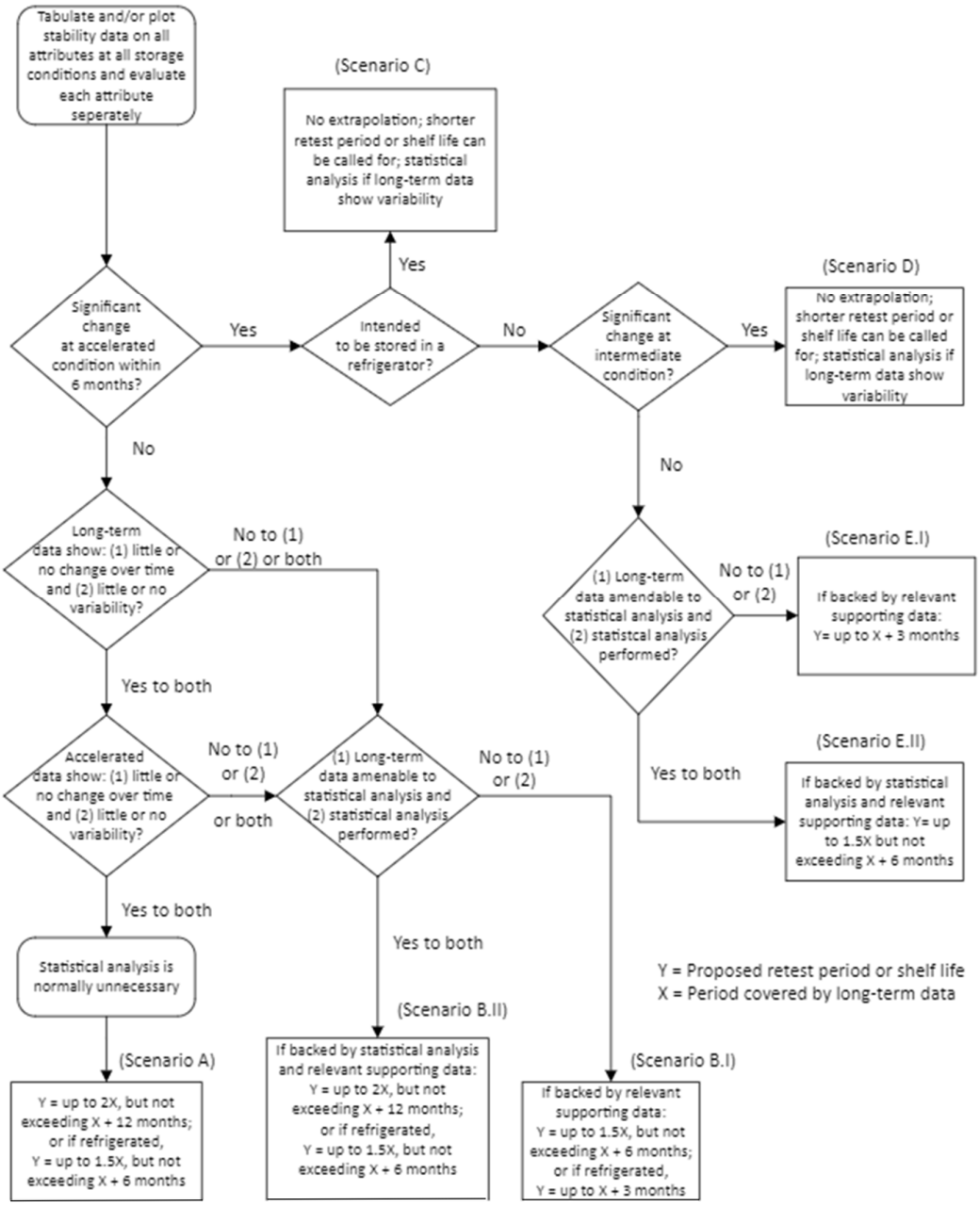
Any shelf life or re-test period proposed based on extrapolation should be verified by additional long-term stability data as these data become available.

13.2.5 Extrapolation for Synthetic Chemical Entities

A systematic approach using a decision tree (Figure 4) is provided as a tool for appropriate data extrapolation beyond the period covered by long-term stability data. The decision tree is intended to apply to synthetic chemical entities that are stored long-term at room temperature or refrigerated conditions and that have stability data at an accelerated storage condition in addition to the long-term stability data. The decision tree is not intended for other products or other long-term conditions (e.g., biologicals or frozen storage). The decision tree provides a complementary approach to the statistical analysis of long-term stability data. The decision tree approach may provide some limited extrapolation though greater extrapolation beyond these stated limits may be possible using other modelling methodologies (refer to Annex 2 –Stability Modelling).

To use the decision tree, the variability between and within batches should allow reasonable confidence that the stability profile meets the attribute specification at the proposed re-test period or shelf life under the recommended storage conditions. The term “room temperature” refers to the general customary environment and should not be inferred to be the storage statement for labelling (refer to Section 14 – Labelling).

Figure 4: Decision Tree for Data Evaluation for Re-test Period and Shelf Life Estimation for Synthetic Chemical Entity Drug Substances and Drug Products (excluding frozen products)



When the decision tree is used for extrapolation, each attribute on the shelf life specification should be systematically evaluated. The assessment should begin with any significant change at the accelerated condition and, if appropriate, at an intermediate condition, and progresses through the trends and variability of the long-term data. The circumstances are delineated under which extrapolation of re-test

period or shelf life beyond the period covered by long-term data can be appropriate. If any attribute that is not quantifiable shows potential for significant change at the accelerated storage condition, then the decision tree cannot be used.

The following subsections describe the decision tree approach, and the scenarios illustrated.

13.2.6 No Significant Change at Accelerated Condition

Where no significant change occurs at the accelerated condition, the re-test period or shelf life would depend on the nature of the long-term and accelerated data. This applies to room temperature and refrigerated drug substances and drug products where no significant change occurs at the accelerated condition.

13.2.6.1 Long-term and Accelerated Data Show Little to No Change Over Time and Little or No Variability (Scenario A)

Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it might be apparent that the drug substance or product will remain well within the acceptance criteria for that attribute during the proposed re-test period or shelf life. In these circumstances, a statistical analysis is normally considered unnecessary but justification for the omission should be provided. Justification can include a discussion of the change pattern or lack of change, relevance of the accelerated data, mass balance, and/or other supporting data. Extrapolation of the re-test period or shelf life beyond the period covered by long-term data can be proposed. The proposed re-test period or shelf life can be up to two times for products stored at room temperature, but should not be more than 12 months beyond, the period covered by long-term data. For refrigerated drug substances or drug products, if the long-term and accelerated data show little change over time and little variability, the proposed re-test period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond the period covered by long-term data.

13.2.6.2 Long-term or Accelerated Data Show Change Over Time and/or Variability (Scenario B)

The decision tree approach considers the significance of change over time under accelerated and long-term storage conditions and method variability. For a synthetic chemical drug substance, a significant change is when an attribute exceeds specification at the accelerated condition within 6 months or long-term storage condition within the intended shelf life or re-test period. For drug product, a significant change has additional considerations applicable to synthetic chemical products including:

(1) 5% change in assay from its initial value

(2) failure to meet the specification for degradation products, physical attributes (e.g., colour, phase separation, re-suspendability, caking, hardness) and, when applicable functionality tests (e.g., dose delivery per actuation);

and for certain dosage forms:

(3) failure to meet specification for pH

(4) failure to meet specification for dissolution testing

With respect to physical attribute changes, the following can be expected to occur at the accelerated condition and would not be considered significant change that calls for intermediate testing if there is no other significant change:

- softening of a suppository that is designed to melt at 37°C, if the melting point is clearly demonstrated,
- failure to meet acceptance criteria for dissolution of a gelatine capsule or gel-coated tablet if the failure can be unequivocally attributed to cross-linking.

However, if phase separation of a semi-solid dosage form occurs at the accelerated condition, testing at an intermediate condition should be performed. Potential interaction effects (e.g., other drug product components) should also be considered in establishing that there is no significant change.

For product intended to be stored at room temperature, when a significant change is observed or anticipated at a particular accelerated storage condition, consider including an intermediate storage condition in the protocol and for the data evaluation. An appropriate intermediate storage condition, as applied to a synthetic chemical entity, depends on the climatic zones intended for the product (refer to Section 7 – Storage Conditions).

If the long-term or accelerated data for an attribute show change over time and/or variability within a factor or among factors (e.g., strength, container size and/or fill), statistical analysis of the long-term data can be useful in establishing a re-test period or shelf life. When there are differences in stability observed across batches or among other factors or factor combinations (e.g., strength, container size and/or fill) that preclude the combining of data, the proposed re-test period or shelf life should not exceed the shortest period supported by any batch, other factor, or factor combination. Alternatively, where the differences are readily attributed to a particular factor (e.g., strength), different shelf lives can be assigned to different levels within the factor (e.g., different strengths). A discussion should be provided to address the cause for the differences and the overall significance of such differences on the product. Extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

13.2.6.3 Data not amenable to statistical analysis (Scenario B.1)

Where long-term data are not amenable to statistical analysis (e.g., colour, clarity using qualitative or semi-quantitative methods), but change over time and relevant supporting data are provided, the

proposed re-test period or shelf life at room temperature storage can be up to one and-a-half times but should not be more than 6 months beyond the period covered by long-term data. For refrigerator storage, the proposed re-test period or shelf life can be up to 3 months beyond the period covered by long-term data.

13.2.6.4 Data amenable to statistical analysis (Scenario B.II)

If long-term data are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, it can be appropriate to propose a re-test period or shelf life when stored at room temperature of up to twice but not more than 12 months beyond the period covered by long-term data, when the proposal is supported by the result of the analysis and relevant supporting data. For refrigerated chemical entities, where statistical analysis is performed, the proposed re-test period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data.

13.2.7 Significant Change at Accelerated Condition

Where significant change occurs at the accelerated condition, the re-test period or shelf life would depend on the storage condition (room temperature or refrigerated) and if stability data at an intermediate condition are available.

13.2.7.1 Significant Change at Accelerated Condition (refrigerated storage) (Scenario C)

For refrigerated storage, if significant change occurs at the accelerated storage condition, the proposed re-test period or shelf life should be based on the long-term data and extrapolation is generally not considered appropriate. Intermediate conditions are also not considered applicable for products stored at refrigerated storage conditions. In addition, a re-test period or shelf life shorter than the period covered by long-term data could be proposed in a science- and risk-based manner. If the long-term data show variability, verification of the proposed re-test period or shelf life by statistical analysis can be appropriate.

13.2.7.2 Significant Change at Accelerated Condition and Significant Change at Intermediate Condition (room temperature storage) (Scenario D)

Where significant change occurs at both accelerated and the intermediate condition, the proposed re-test period or shelf life should be based on the long-term data and extrapolation is generally not considered appropriate. In addition, a re-test period or shelf life shorter than the period covered by long-term data could be proposed in a science- and risk-based manner. If the long-term data show variability, verification of the proposed re-test period or shelf life by statistical analysis can be appropriate.

13.2.7.3 Significant Change at Accelerated Condition and No Significant Change at Intermediate Condition (room temperature storage) (Scenario E)

If there is significant change at accelerated condition but no significant change at the intermediate condition, extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

13.2.7.3.1 Data not amenable to statistical analysis (Scenario E.I)

When the long-term data for an attribute are not amenable to statistical analysis, the proposed re-test period or shelf life can be up to 3 months beyond the period covered by long-term data, if supported by relevant supporting data.

13.2.7.3.2 Data amenable to statistical analysis (Scenario E.II)

When the long-term data for an attribute are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, the proposed re-test period or shelf life can be up to one-and-half times, but should not be more than 6 months beyond, the period covered by long-term data, when backed by statistical analysis and relevant supporting data.

13.2.8 Extrapolation for Chemical Entities when Stored Frozen

When a drug substance or product is stored frozen, with no observable or no statistically significant change over time for the available data of all quality attributes monitored at the recommended storage conditions or a minor change that remains well within the acceptance criteria, extrapolation may be considered based on appropriate prior knowledge and enhanced stability modelling (Annex 2 –Stability Modelling).

13.2.9 Extrapolation for Biologicals

Extrapolation beyond the period covered by available long-term primary stability data may be considered for a well characterised biological drug substance stored frozen, for which the quality attributes are known, and their corresponding criticality and residual risks evaluated to ensure patient safety. Extrapolation of drug substance shelf life should be limited to one and a half times the available long-term data from the primary stability batches to a maximum of 12 months beyond available long-term data, when justified. Justification should include a risk-based approach to fully support the proposed extrapolation, including data available on batches that have long term data to the end of the proposed shelf life that are analytically comparable to primary batches. Justification should also include statistical analysis (such as using linear regression with 95% confidence limit) of available long-term data on representative batches and primary stability batches to show no statistically significant or meaningful change over time. Any observable trend should also be justified. In addition, the risk assessment should take into consideration other aspects such as, knowledge of the molecule and its

degradation profile, impact of degradation of the molecule on drug product, knowledge of the impact on stability due to the rate of freezing and thawing of the drug substance, the container/closure system, drug substance concentration and formulation to support the extrapolation.

Alternative approaches can be proposed and justified for extrapolation and/or shelf life prediction based on appropriate prior knowledge and enhanced stability modelling (Annex 2 –Stability Modelling).

The general principles outlined here for drug substance extrapolation may be applicable to drug product extrapolation, however, due to increased risk, applicants are encouraged to seek agreement with regulatory authorities on the extrapolation proposal and accompanying justification that includes potential impact to patient safety and efficacy. Additionally, for biological drug products, applicants are encouraged to consider enhanced modelling techniques as described in Annex 2 – Stability Modelling.

For biologicals and synthetics, when the proposed shelf life is extrapolated beyond available long-term data from primary stability studies, the primary stability studies should be continued post-approval to confirm the shelf life with long-term data. The ongoing monitoring/trending of stability data should be managed by the manufacturer's PQS. The PQS should be capable of detecting and managing any confirmed changes in stability trend and out of specification results with appropriate corrective action and preventive actions (CAPA) as described in ICH Q10, relevant to any extrapolation being applied.

13.3 Data Evaluation for Multi-factor, Full-design Studies

The stability of the drug product, or drug substance if applicable, could differ to a certain degree among different factor combinations in a multi-factor, full-design study, for example, products with different fill volumes or content and different container dimensions. Two approaches can be considered when analysing such data.

- To determine whether the data from all factor combinations (e.g., fill volume and container dimensions such as vial size), support the proposed shelf life for each combination of drug product presentation.
- To determine whether the data from different factor combinations can be combined for an overall estimate of a single shelf life that applies to each presentation.

A statistical model that includes all appropriate factors and factor combinations may be constructed and the shelf life should be estimated for each factor and for all factor combinations to support the product shelf life.

If all shelf lives estimated by the aforementioned statistical model are longer than the proposed shelf life, further model building is considered unnecessary, and the proposed shelf life will generally be

appropriate for all combinations of factors. The stability data from different factors should not be combined unless supported by scientific understanding and statistical testing.

13.3.1 Testing to Combine Batch Data per Individual Combination

If each factor combination is considered separately, the stability data can be statistically tested to combine those batch data for each individual combination. The shelf life for each non-batch factor combination can be estimated separately by applying the procedure described for single factor, full design (Refer to Annex 2, Section A2-1 – Statistical Evaluation of Stability Data from Single or Multi-Factor Study Designs). For example, for a drug product available in two strengths and four container sizes, eight sets of data from the 2 x 4 strength-size combinations can be analysed and eight separate shelf lives should be estimated accordingly. For a single shelf life across the strengths and container sizes, the shortest (worst-case) estimated shelf life among all factor combinations should become the shelf life for the product. However, this approach does not consider all the available data from all factor combinations, thus generally resulting in shorter shelf lives than the approach that combines batches for all factors and factor combinations.

13.3.2 Testing to Combine Data for All Factors and Factor Combinations

If the stability data are tested to combine all factors and factor combinations and the results show that the data can be combined, a single shelf life across all combinations and longer than that estimated based on individual factor combinations may be proposed. The shelf life is longer because the width of the confidence limit(s) for the mean will become narrower as the amount of data increases when batches, strengths, container sizes and/or fills, etc. are combined into a single analysis of covariance (e.g., ANCOVA).

Analysis of covariance (e.g., ANCOVA) can be employed to test the difference in slopes and intercepts of the regression lines among factors and factor combinations. The purpose of the procedure is to determine whether data from multiple factor combinations can be combined for the estimation of a single shelf life that could apply to all 8 presentations for the previous example (refer to Section 13.3.1 - Testing to Combine Batch Data per Individual Combination).

The full statistical model should include the y-intercept and slope terms for all main effects and interaction effects and a term reflecting the random error of measurement. If it can be justified that the higher order interactions are very small, there is generally no need to include these terms in the model. In cases where the analytical results at the initial time point are obtained from the dosage form prior to its packaging, the effect of container is taken into account in each measure as comparisons are made to the initial time point analysed prior to packaging.

The tests to combine data should be specified to determine whether there are statistically significant differences among factors and factor combinations. Generally, the statistical tests for covariance should be performed in a proper order such that the slope terms are tested before the intercept terms and the interaction effects are tested before the main effects. For example, the tests can start with the slope and then the intercept terms of the highest order interaction and proceed to the slope and then the intercept terms of the simple main effects. The most reduced model, obtained when all remaining terms are found to be statistically significant, can be used to estimate the shelf life.

All tests should be conducted using appropriate levels of significance (refer to Annex 2 – Stability Modelling). Typically, a significance level of 0.25 can be used for batch-related terms, and a significance level of 0.05 can be used for non-batch-related terms. If the tests show that the data from different factor combinations can be combined, the shelf life can be estimated according to the procedure described for a single batch (refer to Section 13.2.1 – Linear Regression for an Individual Batch), using the combined data.

If the tests show that the data from certain factors or factor combinations should not be combined, then a single shelf life can be estimated based on the shortest estimated shelf life among all levels of factors and factor combinations remaining in the model.

After model selection and implementation, model lifecycle consideration should be considered per Annex 2 - Stability Modelling, Section 2.7 – Risk Management and Model Lifecycle Considerations.

13.4 Data Presentation

The applicant should follow ICH M4Q for data presentation expectations. In general, for stability data, data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data. The values of quantitative attributes at all time points should be reported as measured and as calculated to support the label claim, where applicable. If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified.

14 LABELLING

Guidance for labelling and storage statements for drug substances and drug products are provided below. Note that the same principles should be applied to stored intermediates when applicable.

A storage statement should be established for the labelling based on the evaluation of stability data with respect to the climatic zone where the drug substance and/or drug product are intended to be stored, shipped, or used. When applicable, storage statements should reflect information related to the in-use period and storage conditions. It is recommended that an appropriate temperature range be included on the label. Terms such as “ambient conditions’ or “room temperature” should be avoided on the label.

Where applicable, specific instructions should be provided within the labelling, particularly for drug substances, intermediates and drug products that cannot tolerate freezing and thawing, exposure to light or humidity. Additional information may be included on the label for drug products with an established short-term storage condition (refer to Section 10 – Short-Term Storage Conditions).

There should be a direct link between the label storage statements and the demonstrated stability. An expiration date/re-test date, derived from the stability information, should be displayed on the container closure system labelling, as appropriate.

14.1 Excursions Outside of a Labelling Claim

The quality attributes of pharmaceutical drug substances and drug products can be impacted by the extent of the environmental factors experienced during handling, transport, and storage. Those impacts should be evaluated and specified instructions may be provided on the product labelling.

Transient temperature excursions outside of the label storage conditions, may be acceptable if justified and supported by stability data. An assessment of the risk and impact of handling, transport, and storage excursions outside the label claim at various stages throughout the overall supply chain requires a comprehensive knowledge of the supply chain and an understanding of a drug substance and drug product's stability profile. Data from stability studies, including accelerated studies, stress testing (Refer to Section 2 – Development Studied Under Stress and Forced Conditions), or transport simulation studies (when appropriate) can be used to evaluate the effects of an excursion on the drug substance or drug product. Additionally, statistical evaluation or modelling can be leveraged to evaluate the impact of a storage condition excursion, provided sufficient knowledge of the degradation pathway is available and fits an appropriate model. Each excursion should be documented and handled within the corresponding quality management system or appropriate risk assessment.

15 STABILITY CONSIDERATIONS FOR COMMITMENTS AND PRODUCT LIFECYCLE MANAGEMENT

Consistent with ICH Q8, the product lifecycle includes all phases in the life of a drug substance and drug product from the initial development through the marketing until the product's discontinuation. Lifecycle management in the context of stability includes initial stability testing and re-test period and shelf life determination, ongoing (annual) stability testing, and stability studies supporting post-approval changes or commitments over a product's lifecycle. This also includes the introduction of new dosage forms or new strengths/concentrations. Commitment stability studies include studies to confirm the initially proposed re-test period/shelf life for commercial manufacture. This section also provides guidance on stability studies necessary to support the product lifecycle after an initial re-test period or shelf life has been established in the regulatory submission. While guidance in this section is focused on product lifecycle management of drug substances and drug products, general principles may also apply to intermediates that require studies to support re-test period/shelf life or holding times.

In cases where data from commitment stability studies fall outside the acceptance criteria, as confirmed through quality investigation, the stability commitment should include a proposed action to the competent authority in accordance with regional requirements.

15.1 Commitment Stability Studies

Commitment stability studies are conducted under the accelerated, intermediate, or long-term storage conditions (as applicable) to establish or confirm the initial re-test period or shelf life. Where the primary stability studies for a drug substance or drug product do not cover the proposed re-test period or shelf life period granted at the time of initial approval, a commitment should be made to continue the stability studies to confirm the proposed re-test period or shelf life. If applicable, data supporting the claim that manufacturing scale does not impact stability of the product should be provided for regulatory assessment. When all the batches used in the primary stability studies are production batches and stability data cover proposed re-test period and/or shelf life, a post-approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the regulatory submission includes long-term data from stability studies less than the re-test period/shelf life for at least three production batches, a commitment should be made to continue these studies through the proposed re-test period/shelf life.
- If the regulatory submission includes data from stability studies on fewer than three production batches, a commitment stability study should be conducted to generate stability data on at least three production scale batches in total. Commitment stability studies under the long-term storage conditions should be initiated or continued though the proposed re-test period and/or/ shelf life and, if applicable, under the accelerated storage conditions through to 6 months.

- For synthetics, if the regulatory submission does not include stability data on production batches, a commitment stability study should be conducted to generate stability data on at least three production scale batches. Commitment stability studies under the long-term storage conditions should be initiated and continued through the proposed re-test period and/or shelf life and, if applicable, under the accelerated storage conditions through to 6 months.

The commitment stability study protocol should be the same as that for the primary stability study, unless otherwise scientifically justified. Continuation or application of new bracketing or matrixing approaches in the commitment stability studies for the stability commitment should also be justified as discussed in Annex 1 - Reduced Stability Protocol Design.

15.2 Ongoing Stability Studies

Ongoing stability studies are conducted under long-term storage conditions on an annual basis to ensure the consistency of stability related quality attributes at the commercial storage conditions over the product lifecycle. These studies also allow for the monitoring of the stability characteristics and examine trends in the stability data to confirm the appropriate storage conditions relevant for the product and to confirm a re-test period or a shelf life.

In accordance with the general principles in ICH Q7, at least one production batch of the drug substance and one production batch of each strength of the drug product covering the container closure systems should be added to the ongoing stability program per year (unless none is produced that year). Ongoing stability studies are generally managed within the PQS unless a regulatory authority expects additional submission of the information and data. Each production site should maintain an ongoing stability programme in accordance with GMPs. Reduced designs (as discussed below and in Annex 1- Reduced Stability Protocol Design) can be applied where justified.

Ongoing stability studies are not required to align with the primary stability protocol; however, testing should continue through to the end of the re-test period or shelf life. As product knowledge is gained, the applicant may consider removal of testing of attributes not related to stability and/or reduce testing timepoints based on risk assessment as detailed in Section 3 - Stability Protocol Design. Reductions, including bracketing and/or matrixing approaches, based on stability knowledge and risk assessment should be justified in the regulatory submission, where applicable, as detailed in Annex 1 (Reduced Stability Protocol Design). Reduced protocol designs applied in the original regulatory submission should be followed until there is a change in configuration (e.g., strength/concentration). Any change in the reduced design post-approval should be evaluated for its impact to the product quality prior to modifying the annual stability protocol. While the testing intervals listed during product development may be appropriate in the pre-approval stage, reduced testing may be appropriate after approval where

data are available that demonstrate adequate and consistent stability. Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to propose and justify, where applicable, a protocol which supports the reduction or elimination of specific testing (e.g., 9-month testing interval) or certain attributes (e.g., orthogonal testing) for post-approval, long-term studies.

15.3 Product Lifecycle Stability Studies

Product lifecycle stability studies are conducted under the accelerated, intermediate, or long-term storage conditions (as applicable) to support product lifecycle changes by assessing whether the change has an impact on any stability related quality attributes of the commercial drug substance or product under the labelled storage, handling and use conditions. A risk assessment should be conducted (refer to Section 3 – Stability Protocol Design and Annex 1 – Reduced Stability Protocol Design) and can be used to justify the change and determine the need and extent of studies required to support changes after approval in compliance with regional requirements. A post-approval change could fall into one of the following scenarios that are based on the nature and impact of the change, stability data requirements and where the re-test/shelf life establishment could change:

- *Scenario 1:* A stability risk assessment indicates the proposed changes will *not have an impact* on the stability profile (e.g., change to a comparable analytical procedure, change in outside cap colour). Stability data in this case is unnecessary and the re-test period or shelf life will not be re-established. Maintained product stability would be confirmed as part of the Ongoing Stability Programme.
- *Scenario 2:* The proposed changes *may potentially impact* the stability profile (e.g., manufacturing process change, change in formulation). A stability study, a stability risk assessment, or a combination thereof may be appropriate to support this change. The risk assessment process may include a well-designed study to determine whether additional formal stability studies or other supportive stability studies are necessary. The assessment should establish whether the re-test period/shelf life and storage condition may be maintained or if they should be re-established.
    - If the proposed changes have a demonstrated impact that can reduce or extend the re-test period/shelf life based on the preliminary stability results, then a re-test period/shelf life and storage condition may need to be re-established per recommendations in Section 3 - Stability Protocol Design through Section 7 - Storage Conditions.
    - If the proposed change is expected to have a low impact but formal stability studies are warranted based on preliminary data and risk assessment, a commitment should be made to continue these stability studies through the re-test period/shelf life and the re-test period or shelf life does not need to be re-established.

- If the proposed change is demonstrated through the risk assessment and/or a well-designed stability study (including analytical comparability according to ICH Q5E for biological products), to not impact the re-test period or shelf life, then this assessment and/or data may be used to justify that formal stability studies are not needed to retain the current re-test period or shelf life (e.g., change in compendial excipient supplier).
- If a risk assessment or an initial set of stability results do not allow for an understanding of the impact to the re-test period/shelf life, the re-test period/shelf life and storage condition may need to be re-established based on the post-change stability data.

- Product lifecycle stability studies intended to extend the re-test period or shelf life should align with the principles outlined for primary stability (e.g., for setting re-test period/shelf life). Justification should be provided when a shelf life reduction is proposed as a post-approval change. This justification should only be based on scientific reasons.

In most circumstances, stability evaluation is generally expected in the context of the specific change and should include assessment of impact on drug substance, intermediate and/or final drug product. Additional scientific, risk-based considerations and approaches for identifying stability-related quality attributes, use of appropriate tools to evaluate the impact of the intended change and developing strategies for confirmatory stability studies supporting stability for post-change material are included in ICH Q12, Chapter 9 (Stability Data Approaches to Support the Evaluation of CMC Changes) and recommendations for post-approval changes. For biologicals, after successful demonstration of analytical comparability according to ICH Q5E including the stability profile, the shelf life of the pre-change material can be assigned to the post-change material. If successful demonstration of analytical comparability is not achieved, additional stability studies would be needed.

In some instances, a stability protocol may include additional time points beyond a proposed shelf life to allow shelf life extensions in the future (e.g., to avert supply management issues). An extension of the approved shelf life based on acceptable stability data from a minimum of 3 production or primary batches may be submitted to allow a longer shelf life.

The applicant should apply an appropriate stability strategy that demonstrates the established re-test period/shelf life and storage conditions are still accurate. In such cases, an appropriate stability strategy may include:

- A targeted stability study that focuses on the potentially impacted stability related quality attributes and re-test period/shelf life limiting attributes.

- The use of comparative accelerated/stress and/or predictive stability studies (e.g., modelling, including extrapolation, or stability bridging study for biological product) to demonstrate the understanding from the process/product change.
- A risk assessment demonstrating that an understanding of the impact to any stability related quality attributes can support limited real-time data for post-change material while claiming the same re-test period/shelf life as the pre-change material.
- A full evaluation of stability related quality attributes through long-term studies. This may be necessary when the impact of the change is not well understood or demonstrated.

Reduced protocol designs may be applied for drug products with multiple commercial presentations where stability performance is generally well understood. For example, a worst-case approach may be applied to products with multiple bottle configurations, where the configuration with the highest moisture vapor transmission rate (MVTR) is selected for evaluation (refer to Annex 1 – Reduced Stability Protocol Design). Reduced protocol design considerations may also apply to photostability or in-use studies supporting changes such as primary/secondary packaging or in-use and should follow the same considerations as discussed above and in Section 8 - Photostability and Section 11 In-Use Stability.

If specific tests or timepoints from the primary stability studies had been removed for the ongoing stability protocol, these may need to be restored for the stability studies used to support a post-approval change.

15.4 Stability Studies to Support New Dosage Forms and New Strengths/Concentrations

This section addresses the recommendations on what should be submitted regarding stability of a new dosage form or a new strength/concentration by the owner of the original regulatory submission. A new dosage form or strength/concentration contains the same drug substance as included in the existing, approved drug product. Within scope of a new dosage form are new products with different administration route (e.g., oral to parenteral, intravenous to subcutaneous), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet, lyophilised to liquid product) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension, vial to prefilled syringe).

Stability protocols for new dosage forms or new strengths/concentrations should generally follow the guidance for primary stability studies (refer to Table 1). In certain justified cases, based on prior knowledge and an established stability profile, a science- and risk-based, reduced stability protocol at submission may be acceptable (e.g., 6 months accelerated and 6 months long term data for a new dosage form for a synthetic chemical entity per Table 1). In cases where the existing commercial data are

relevant to the shelf life of the new dosage form or the new strength/concentration, a risk assessment with an appropriate justification and additional supporting information (e.g., predictive data, comparative bridging data and/or prior knowledge) should be provided. In these cases, a commitment stability study would also be expected in accordance with the principles discussed in Section 15.1 – Commitment Stability Studies.

16 GLOSSARY

Accelerated Studies: Testing conducted on drug substance and drug product that have been stored under conditions intended to increase the rate of physical, chemical and/or biochemical change (temperature and when applicable humidity), over a defined time period. These data can be used to gain product knowledge and to support extrapolation, re-test period or shelf life determination and to evaluate the impact of excursions outside the label storage conditions.

AI-ML: Artificial Intelligence Machine Learning

ANCOVA: Analysis of covariance

ATMP: Advanced Therapy Medicinal Products

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are functional (e.g., combination of a drug product with a medical device) or intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system. For the drug substance the container closure system is the packaging proposed for storage and distribution.

Commitment stability studies: Stability studies conducted under the accelerated, intermediate, or long-term storage conditions (as applicable) to establish or confirm the initial re-test period or shelf life in accordance with a commitment in the regulatory submission.

CAPA: Corrective and Preventive Actions (ICH Q12)

CM: Continuous Manufacturing (ICH Q13)

CQA: Critical Quality Attributes (ICH Q8)

Degradation Product: Molecular variants or impurities resulting from chemical or biochemical changes in the desired product or product-related substances brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the container closure system and/or device component. Such changes may occur as a result of manufacture and/or storage (e.g., hydrolysis, deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances or product-related impurities.

DS: Drug Substance

DP: Drug Product

Full design stability protocol: A protocol which includes at least three batches of the drug substance or at least three batches of each strength or concentration of the drug product covering the container closure systems for every combination of all design factors and tested at all time points.

Formal Stability Studies: Primary, commitment, ongoing or product lifecycle stability studies conducted under the accelerated, intermediate, or long-term storage conditions (as applicable) to establish or confirm a re-test period or a shelf life.

GMP: Good manufacturing practice

IgG: Immunoglobulin G

Impermeable Container: Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminium tubes for semi-solids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solids.

Impurity: Any component of the drug substance or drug product which is not the synthetic chemical or biological entity defined as the active ingredient, excipient, or other additives to the drug product. The source of the impurity could be product or process related.

Intermediate: A material that is produced during a manufacturing process, which is not the final drug substance or the final drug product. Intermediates are identified by a manufacturer, who should establish and justify a control strategy to assure the intermediate's stability within conditions of the manufacturing process. Bulk drug products are considered drug product intermediates.

LED: Light-emitting diode

Long-term Testing: Stability studies under the recommended long-term storage condition for the re-test period or shelf life proposed (or approved) for labelling. Long-term testing results in real time data obtained at the long-term storage condition.

Mass balance: For synthetic chemical entities, the process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Mean kinetic temperature: A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (28) can be used.

Model verification: The process of ensuring the model is implemented as intended. For example, confirmation that the modelled data for the initially proposed shelf life or re-test period are comparable to confirmatory experimental data.

Model validation: The process of determining the suitability of a model by challenging it with independent test data and comparing the results against predetermined performance criteria.

NMT: Not More Than

Ongoing stability studies (also referred to as annual stability studies): Stability studies conducted under long-term storage conditions on an annual basis to ensure the consistency of stability related quality attributes at the approved storage conditions over the product lifecycle. These studies also allow for the monitoring of the stability characteristics and examine trends in the stability data to confirm the appropriate storage conditions relevant for the product and to confirm a re-test period or a shelf life.

Open Dish Study: A study conducted without the protection of the immediate container, representing a worst-case scenario under controlled conditions.

Pilot Scale Batch: A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for synthetics chemical entities in solid dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 units, whichever is the larger, unless otherwise adequately justified. For biologics, the steps of upstream and downstream processing should be identical except for the scale of production.

PQS: Pharmaceutical Quality System

Primary Batch: A batch of a drug substance or drug product used in a primary stability study.

Primary Stability Studies: Stability studies conducted under the accelerated and long term (and, where applicable, intermediate) storage conditions undertaken on primary stability batches to establish a re-test period or a shelf life. Where appropriate, the primary stability studies may be conducted on non-production scale batches.

Prior Knowledge: Prior knowledge refers to existing knowledge and includes internal knowledge (e.g., development and manufacturing experience), external knowledge (e.g., scientific and technical publications, including vendors' data, literature and peer-reviewed publications), or the application of established scientific principles (e.g., chemistry, physics and engineering principles).

Production Batch: A batch of a drug substance or drug product manufactured at production scale using production equipment and process in the commercial production site as specified in the regulatory submission.

Product lifecycle stability studies: Stability studies conducted under the accelerated, intermediate, or long-term storage conditions (as applicable) to support product lifecycle changes by assessing whether the change has an impact on any stability related quality attributes of the commercial drug substance or product under the labelled storage, handling and use conditions.

RH: Relative Humidity

Re-test Date: The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Re-test Period: The re-test period is a period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in manufacture of a given drug product, provided the drug substance has been stored under the defined conditions. After this period, a batch of drug substance can be re-tested for compliance with its specification and then used immediately for manufacture of drug product. A re-test period is normally applicable to synthetic drug substances and may be applicable to certain well-characterised biological drug substances.

Semi-permeable Containers: Containers that allow the passage of solvent or gas, while preventing solute loss. Examples of semi- permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenteral (LVPs), and LDPE ampoules, bottles and vials.

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

Significant Change for Synthetics: Significant change for a drug substance is defined as failure to meet its specification. In general, “significant change” for a drug product is defined as: (1) A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures (e.g., for antibiotics); (2) Any degradation product exceeding its acceptance criterion; (3) Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g., colour, phase separation, re-suspendability, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions; and, as appropriate for the dosage form; (4) Failure to meet the acceptance criterion for pH; (5) Failure to meet the specification for dissolution testing; or, (6) A 5% loss in water from its initial value for products stored in semi-permeable containers.

Storage Condition Tolerances: The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies.

Stress Studies: Studies undertaken to assess the effect of stress conditions on the drug substance and/or drug product which can be divided into two categories:

1) Studies conducted under stress conditions that are more severe than the accelerated conditions, but not necessarily intended to deliberately degrade the sample, which may be useful in gaining product knowledge and evaluating the effect of excursions outside the label storage conditions.

2) Studies conducted under forced degradation conditions that are intended to deliberately degrade the sample (such as elevated temperature, humidity, pH, oxidation, agitation and light) and may be used to: investigate the potential degradation pathways; gain product knowledge; understand the intrinsic stability of drug substance; and used to develop and confirm stability-indicating nature of the analytical procedure.

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

Supportive stability studies: Ancillary stability studies that are conducted (as applicable) to support the practical use of the product (including label claims) or a re-test period or a shelf life (e.g., photostability, in-use, short-term studies and studies to support excursions or modelling). Data to support short-term storage conditions, where relevant, may be provided as part of the primary stability studies.

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18 ANNEXES

Annex 1 Reduced Stability Protocol Design

A1-1 Introduction

This annex is intended to address recommendations on the application of reduced stability protocol designs conducted in accordance with principles outlined in the core guideline.

A reduced stability protocol design is one in which samples for every factor combination are not all tested at all time points.

The reduced stability designs presented below may be proposed for any formal stability study protocol, i.e., primary, commitment, ongoing (annual), product lifecycle. Implementation of some strategies requires a strong understanding of product stability performance and risks and may be more suitable for lifecycle applications or where prior knowledge may be leveraged. If a reduced protocol design is introduced after the original marketing authorisation, change management procedures should be followed (refer to ICH Q10) in accordance with regional requirements.

This annex provides guidance on bracketing and matrixing study designs and other science- and risk-based reduced stability design strategies. Specific principles are defined for situations in which reduced stability strategies can be applied. Sample designs are provided for illustrative purposes and should not be considered the only, or the most appropriate, designs in all cases.

A1-2 General Principles for Reduced Stability Designs

Any reduced design should be able to meet the objective of the study with a defined and acceptable risk as compared to a full design. The potential risk associated with a reduced design should be considered (e.g., establishing a shorter re-test period or shelf life than could be derived from a full design due to the reduced amount of data collected).

Reduced designs can be applied to long-term stability studies for most types of drug products, although additional justification should be provided for complex products (e.g., a drug delivery system where there are many potential drug-device interactions, certain biological products). For the study of drug substances, matrixing is usually of limited utility and bracketing is generally not applicable; however, reduced time points and/or attribute testing could be justified where little or no degradation occurs. Additional reduced protocol designs are also discussed and may be most relevant when product and stability knowledge are

high (e.g., to support post-approval changes; Refer to Section 15 – Stability Considerations for Commitments and Product Lifecycle Management).

Whether a reduced design can be applied depends on a number of circumstances, as discussed in detail below. The use of any reduced design should be justified. In certain cases, the condition described in this annex is sufficient justification for use, while in other cases, additional justification should be provided. The type and level of justification in each of these cases will depend on the available supporting data and risk assessment.

The reduced designs discussed below are based on different principles. Therefore, careful consideration and scientific justification should precede the use of more than one reduced design principle together in one design.

If risks are identified during a reduced design study, a change to full testing or to a less reduced design may be implemented with an explanation of the drivers for the increase to the design. Proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change (26-27). Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

A1-3 Reduced Design Approaches

A1-3.1 Bracketing

Bracketing is design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, would be tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Bracketing can be applied to different container sizes or different fills in the same container closure system.

The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the strengths or container sizes and/or fills selected for testing are indeed the extremes.

A1-3.1.1 Design Factors

Design factors are variables (e.g., strength, container size and/or fill) to be evaluated in a study design for their effect on product stability.

A1-3.1.1.1 Strength

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations

whose stability trends could be reasonably considered similar. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of a common blend, (3) liquid formulation of a biological of different concentration or fill volume, unless there are additional considerations for excluding some complex biologicals or live vaccines, (4) solutions and solid dosage forms for oral use of different strengths with formulations that differ only in minor excipients (e.g., colourants, flavourings).

With justification and supporting data, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation.

In cases where different excipients are used among strengths, bracketing generally should not be applied.

A1-3.1.1.2 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 container closure system configurations. Care should be taken to select the extremes by comparing the various characteristics of the container closure system that may affect product stability. Depending on the dosage form and container closure system, the following characteristics may be considered relevant: container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapour permeation rate or oxygen permeation rate per dosage unit or unit fill volume, product contact coating, stopper or closure formulation and coating, as appropriate.

Bracketing can be applied to studies for the same container when the closure varies. Justification could include a discussion of the relative permeation rates of the bracketed container closure systems. Special consideration and justification may be required for drug products stored in semi-permeable containers (refer to Section 7.2.2 – Storage Conditions for Products Packaged in Semi-Permeable Containers).

A1-3.1.2 Design Considerations and Potential Risks

Before a bracketing design is applied, its effect on the re-test period or shelf life estimation should be assessed. If the stability of the extremes is shown to be different, the intermediates 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).

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.

A1-3.1.3 Design Example

An example of a bracketing design is given in **Table A1- 1.** This example is based on a product available in three strengths and three container sizes. In this example, the 15 mL and 500 mL container sizes represent the extremes. The batches for each selected combination should be tested at each time point as in a full design. Note that the example below could represent multiple product types (synthetics and biologicals).

Table A1- 1: Example of a Bracketing Design

Strength		**50 mg**			**75 mg**			**100 mg**		
Batch		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Container size	**15 mL**	T	T	T				T	T	T
	100 mL									
	500 mL	T	T	T				T	T	T

Key: T = Sample tested

A1-3.2 Matrixing

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

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the container closure systems (e.g., inclusion of a foil overwrap).

Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied if justified.

A1-3.2.1 Design Factors

Matrixing designs can be applied to strengths with identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the

same granulation and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colourants or flavourings), (4) biological of different concentration and fill volume, (5) biologicals of different concentration with different size container or pre-filled syringe size, (6) relative amounts of excipients (e.g., minor variation to the concentration of the filler). Justification should generally be based on supporting data. For example, to matrix across two different closures or container closure systems, supporting data could be supplied showing relative moisture vapour transmission rates or similar protection against light. Alternatively, supporting data could be supplied to show that the drug product is not affected by oxygen, moisture, or light.

Other factors for matrixing may be considered if justified, e.g., batches made by using the same process and equipment and container sizes and/or fills in the same container closure system.

A1-3.2.2 Design Considerations

A matrixing design should be balanced as far as possible so that each combination of factors is tested to the same extent over the intended duration of the study and through the last time point prior to submission. However, due to the recommended full testing at certain time points, as discussed below, it may be difficult to achieve a complete balance in a design where time points are matrixed.

In a design where time points are matrixed, all selected factor combinations should be tested at the initial and final time points, while only certain fractions of the designated combinations should be tested at each intermediate time point. In addition, unless justified, data from at least three time points, including initial, should be available for each selected combination through the first 12 months of the study.

For matrixing at an accelerated storage condition, care should be taken to ensure testing occurs at a minimum of three time points, including initial and final, for each selected combination of factors. Thus, matrixing for accelerated studies may have limited application.

When a matrix on design factors is applied, if one strength or container size and/or fill is no longer intended for marketing, stability testing of that strength or container size and/or fill can be continued to support the other strengths or container sizes and/or fills in the design. Stability commitments in accordance with Section 15 – (Stability Considerations for Commitments and Product Lifecycle Management) should reflect the proposed commercial presentations.

A1-3.2.3 Design Examples

Examples of matrixing designs on time points for a product in two strengths (50 mg and 75 mg) are shown in Tables A1-2 and A1-3. The terms one-half reduction and one-third reduction refer to the reduction

strategy initially applied to the full study design for timepoints excluding initial, 12-months and final. For example, a one-half reduction initially eliminates one in every two time points from the full study design and a one-third reduction initially removes one in every three. In the examples shown in Tables 2 and 3, the reductions are less than one-half and one-third due to the inclusion of full testing of all factor combinations at some time points.

Table A1- 2 Example One-Half Reduction Matrix Design on Time Points for a Product with Two Strengths

Time point (months)			0	3	6	9	12	18	24	36
Strength	50 mg	Batch 1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T	T		T
	75 mg	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

Key: T = Sample tested

Table A1- 3 Example One-Third Reduction Matrix Design on Time Points for a Product with Two Strengths

Time point (months)			0	3	6	9	12	18	24	36
Strength	50 mg	Batch 1	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
	75 mg	Batch 1	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

Key: T = Sample tested

Additional examples of matrixing designs for a product with three strengths (50 mg, 75 mg and 100 mg) and three container sizes (15 mL, 100 mL and 500 mL) are given in Tables A1-4 and A1-5. Table A1-4 shows a design with matrixing on time points only and Table 5 depicts a design with matrixing on time points and factors. In Table A1-4, all combinations of batch, strength and container size are tested, while in Table A1-5, certain combinations of batch, strength and container size are not tested.

Table A1- 4 Examples of Matrixing on Time Points for a Product with Three Strengths and Three Container Sizes

Strength	**50 mg**			**75 mg**			**100 mg**		
Container size	**15 mL**	**100 mL**	**500 mL**	**15 mL**	**100 mL**	**500 mL**	**15 mL**	**100 mL**	**500 mL**
Batch 1	T1	T2	T3	T2	T3	T1	T3	T1	T2
Batch 2	T2	T3	T1	T3	T1	T2	T1	T2	T3
Batch 3	T3	T1	T2	T1	T2	T3	T2	T3	T1

Table A1- 5 Examples of Matrixing on Time Points and Factors for a Product with Three Strengths and Three Container Sizes

Strength	**50 mg**			**75 mg**			**100 mg**		
Container size	**15 mL**	**100 mL**	**500 mL**	**15 mL**	**100 mL**	**500 mL**	**15 mL**	**100 mL**	**500 mL**
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	

Key for Table A1- 4 **and** Table A1- 5:

Time-point (months)	0	3	6	9	12	18	24	36
T1	T		T	T	T	T	T	T
T2	T	T		T	T		T	T
T3	T	T	T		T	T		T

T = Sample tested

A1-3.2.4 Applicability and Degree of Reduction

The following, although not an exhaustive list, should be considered when a matrixing design is contemplated:

- knowledge of data variability
- expected stability of the product
- availability of supporting data, including enhanced stability knowledge if available
- stability differences in the product within a factor or among factors

- number of factor combinations in the study and/or
- stability risk assessment, if performed.

Data variability and product stability, as shown by supporting data, should be considered when a matrixing design is applied. If the supportive data show large variability, a matrixing design should not be applied.

If a matrixing design is considered applicable, the degree of reduction that can be made from a full design depends on the number of factor combinations being evaluated. The more factors associated with a product and the more levels in each factor, the larger the degree of reduction that can be considered. However, any reduced design should have the ability to adequately predict the product shelf life.

A1-3.2.5 Potential Risk

Due to the reduced amount of data collected, a matrixing design on factors other than time points generally has less precision in shelf life estimation and yields a shorter shelf life than the corresponding full design. In addition, such a matrixing design may have insufficient power to detect certain main or interaction effects, thus leading to incorrect pooling of data from different design factors during shelf life estimation. If there is an excessive reduction in the number of factor combinations tested and data from the tested factor combinations cannot be pooled to establish a single shelf life, it may be impossible to estimate the shelf lives for the missing factor combinations. The risk may be mitigated through use of supportive stability data.

A study design that matrixes on time points only may be used to detect differences in rates of change among factors and to establish a reliable shelf life. This strategy assumes linearity and full testing of all other factor combinations at both the initial and final time points.

A1-3.3 Knowledge and Risk Based Protocol Reductions

Additional reduced stability protocol designs that are different from bracketing and matrixing approaches may also be applied. Product knowledge and risk-based assessments are used to justify these stability strategies. If the knowledge- and risk-based reduced protocol is used to support a post-approval change, the risk assessment should also consider the potential impact of the change on the stability performance of the product. As discussed in ICH Q12, Chapter 9, there are numerous methods to assess the impact of a change in addition to long-term stability studies.

A1-3.3.1 Design Factors

Where justified, a reduction may be applied to attributes, timepoints, samples and/or storage conditions.

To apply these strategies, the applicant should present an understanding of what attributes are subject to change over the re-test period/shelf life and what conditions might impact their rate of change. This should be supported by data and/or product knowledge and used to conduct a risk assessment that justifies the proposed reductions.

A1-3.3.2 Design Considerations and Potential Risks

Stability risk assessment tools should be developed throughout the product lifecycle in accordance with ICH Q9. The stability understanding used to assess risk may come from multiple sources, including stress testing, accelerated testing, formal stability studies and prior knowledge from product development, e.g., on leachables and container closure integrity.

Quality attributes that are considered low risk for stability testing are those that are unlikely to change on stability and are not critical to safety and efficacy of the product. An example of this is residual solvent content in a crystalline synthetic drug substance, since residual solvent content is assessed at release and will not increase over time and does not have the potential to impact other CQAs. With appropriate justification, these attributes may be removed from the stability protocol.

Certain quality attributes may be removed when the attribute has the potential to change but has been demonstrated not to change over time or is monitored via other quality attributes and the change is established to not have a meaningful impact on quality, safety and efficacy through the re-test period or shelf life. However, to support a future change the impact on the stability of these quality attributes should be assessed and if necessary, reintroduced.

A1-3.3.3 Design Strategies and Examples

Descriptions of protocol reduction strategies and examples of instances where a reduced protocol approach may be applied with justification are provided below. These strategies may be applied to other situations as well when justified.

Reductions from the Primary Stability Protocol for Stability Commitments: Based on overall product knowledge, development data and/or results of the ongoing or completed primary stability study, the applicant may propose to remove attributes, storage conditions and/or timepoints for new protocols. This may be justified if the applicant:

- Demonstrates that the attribute is unchanging on stability, not clinically meaningful, not relevant to the assessment of re-test period or shelf life and not required for monitoring of the quality, safety and efficacy of the drug product after release and during its expected lifecycle.

- Demonstrates how different storage conditions may impact stability and the worst-case storage conditions relevant to the drug substance or drug product are selected for evaluation.
- Demonstrates that specific timepoints are not meaningful for assessment of trends.

Example 1 *– Reduction from Primary Stability Study to the Commitment Study that Confirms Shelf Life for Synthetic Solid Oral Tablet.*

Justification for the reduction from the primary protocol to the commitment protocol to confirm the shelf life (refer to Section 15 Stability Considerations for Commitments and Product Lifecycle Management) below may include historical data and accumulated knowledge supporting:

- lack of change to water activity and microbiological attributes,
- demonstration that trends are not significant justifying removal of the 9- and 18-month timepoints
- knowledge the product is stable when stored at 30 ºC/75 % RH and that this data may be used to represent storage at less strenuous room temperature conditions

Table A1- 6 Example of a Protocol Design for Primary Stability Studies

Storage Condition	**Timepoint (months)**							
	Initial	**3**	**6**	**9**	**12**	**18**	**24**	**36**
25°C/60% RH	A	B	B	B	C	B	C	C
30°C/75% RH		B	B	B	C	B	C	C
40°C/75%RH		B	B					

A: Release Testing

B: Appearance, Assay, Degradation Products, Dissolution, Water Content

C: Appearance, Assay, Degradation Products, Dissolution, Water Content, Microbiological Testing

Table A1- 7 Example of a Protocol Design for Commitment Stability Studies to Confirm Shelf Life

Storage Condition	**Timepoint (months)**					
	Initial	**3**	**6**	**12**	**24**	**36**
30°C/75% RH	A	B	B	B	B	B
40°C/75%RH		B	B			

A: Release Testing

B: Appearance, Assay, Degradation Products, Dissolution

Targeted Stability Designs:

Worst-Case Analysis Strategies*:* When stability characteristics for a product are well understood and a worst-case presentation is predictable, the applicant may design a stability strategy that evaluates the worst-case presentation with the conclusion that other presentations will demonstrate equivalent or better stability performance.

Example 2 - Different Drug Product Concentrations. If it is well-understood and predictable how the relative amounts of drug substance and excipients impact the stability profile for multiple concentrations, a worst-case approach could be proposed to support a reduction to samples. This approach may be justified where the concentration that provides the worst-case effect on stability is assessed. It is inferred based on product knowledge that if suitable stability is demonstrated for the worst-case concentration, the stability for other concentrations would be similar or improved.

Example 3 - Multiple Container Closure System Configurations and/or Fill Volume. If the characteristics of the product in different container sizes and/or with different fills are well understood and their impact on stability related quality attributes are predictable, then a worst-case approach could be proposed to support a reduction to samples. In this example, the configuration that presents the 'worst-case' for product stability is selected for the stability study. It is inferred based on product knowledge that if suitable stability is demonstrated for the worst-case configuration, the stability for other configurations would be similar or improved.

A1-4 Data Evaluation for Reduced Study Designs

The statistical procedures described in Section 13 - Data Evaluation can be applied to the analysis of stability data obtained from any reduced study design.

If a bracketing design is utilised, there is an assumption that the stability of the intermediate strengths or sizes/fills is represented by the stability at the extremes. If the statistical analysis indicates that the stability of the extreme strengths or sizes/fills is different, the intermediate strengths or sizes/fills should be considered no more stable than the least stable extreme. The statistical procedures suitable for multi-factor, full design study can be applied to the analysis of stability data obtained from a matrixing design study. The statistical analysis should clearly identify the procedure and assumptions used. The use of a matrixing design can result in an estimated shelf life shorter than that resulting from a full design.

Where bracketing and matrixing are combined in one design or when an alternative reduced protocol is utilised, the same statistical principles may be applied.

Annex 2 Stability Modelling

General information on selection of batches and minimum stability data at the time of submission and steps towards a comprehensive evaluation of available stability data are presented in Section 3 - Stability Protocol Design, Table 1 and Section 13 - Data Evaluation, respectively. When limited real-time data are available, Section 13.1 - General Considerations may be referenced for general considerations related to establishing an initial re-test or shelf life of drug substance or drug product using the decision tree for synthetics. While shelf life for biological products is generally established based on long-term stability data, enhanced stability modelling approaches could be considered for biological drug substances and drug products using the principles in section 2 of this Annex or using extrapolation principles (refer to Section 13.2.9-Extrapolation of Biologicals) for certain well-characterised biological drug substances with a well understood stability profile. This Annex provides additional and specific recommendations on statistical tools and models to support the use of extrapolation and enhanced stability modelling approaches.

This Annex is structured in two parts, the first provides examples for the statistical tools and models commonly used to assess the data variability between batches for single factor and multi-factor, full design studies to establish re-test period or shelf life. The second part describes enhanced stability models for well-characterised molecules that may be based on empirical fit of stability data to kinetic functions or incorporating prior knowledge into data evaluation.

As a general principle, the least complex statistical model that best describes the data is recommended to be used. Depending on the model and its context of use, the core study design elements that should be a part of any prospective stability modelling strategy include (1) defining the purpose of the model, (2) a description of the model, type of modelling (e.g., mechanistic or empirical) and its components, including specifying what is being estimated, tested for, or predicted, (3) identification of variables and appropriate statistical tools to achieve the stated study objectives, (4) sample size planning, (5) model development and fitting, including justification of the appropriateness of the input data (6) description, relevance and justification for use of product-specific prior knowledge and sources of prior knowledge, (7) model evaluation, including output data, limitations and assessing model robustness, (8) the quantitation and impact of uncertainty in any estimates or predictions providing adequate statistical assurance of any conclusions drawn (e.g., confidence, tolerance or prediction intervals) (9) model validation and verification with real-time data (10) plans for ongoing model monitoring and lifecycle considerations, as needed and (11) the risk management strategy if differences are observed between the predicted shelf life and actual shelf life based on confirmatory data. Consequently, its usage can be expected to be constrained by the modelling method, input or output data, conditions evaluated, etc., and should not be applied to conditions

outside the model's validated range, including different molecules, without a mechanistic understanding or robust scientific justification based on relevant prior knowledge. Refer to ICH Q8-10 Points to Consider for additional general principles related to model development, validation and verification. Models should be managed through a pharmaceutical quality system (PQS) after successful validation and verification.

A2-1 Statistical Evaluation of Stability Data from Single or Multi-factor Study Designs

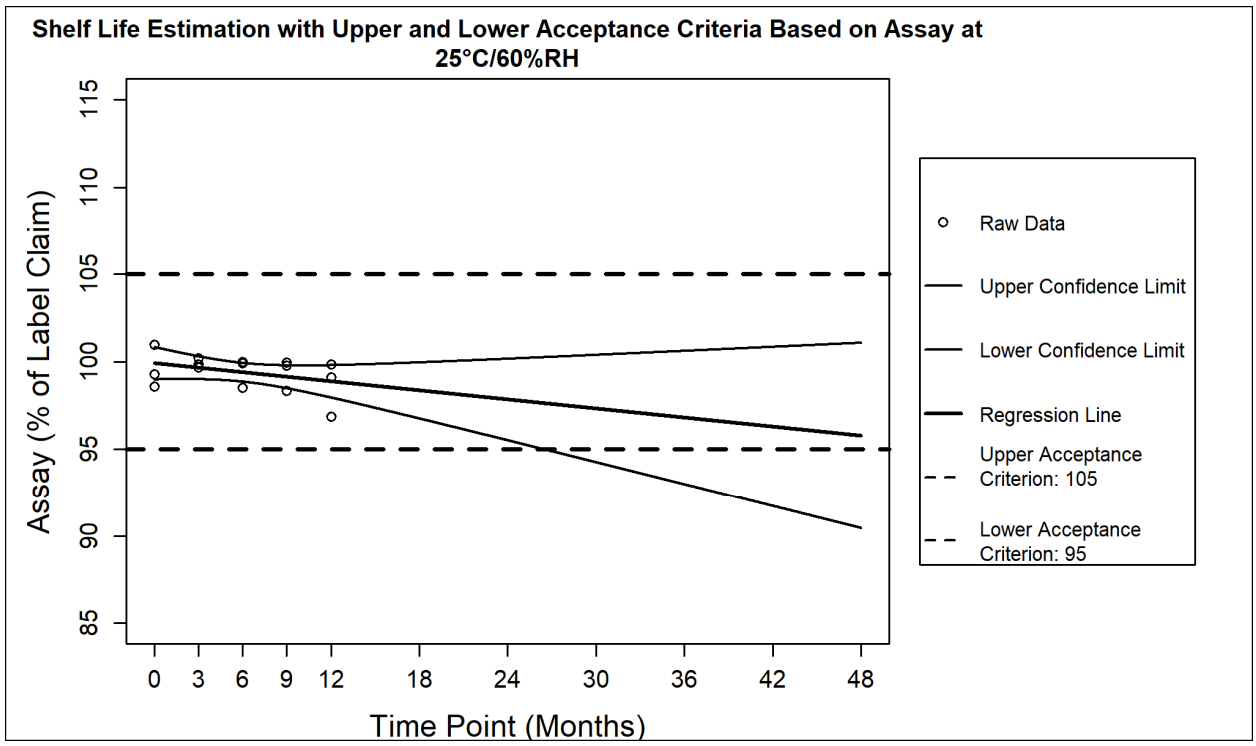
In this section of the Annex, data evaluation is discussed for (A) single factor and (B) multi-factor, full-design studies; where a single factor could be the batches used for a single product and multi-factors includes different fill volumes, concentrations, container dimensions etc, to set re-test period or shelf life when the stability protocol is not reduced by bracketing or matrixing (21). When data from non-primary batches are used, the representativeness of the process, container closure system and analytical procedure should be justified, including the impact of any differences, in the context of the modelling strategy being proposed. Data from primary stability batches need to meet criteria outlined in Section 3 – Stability Protocol Design and elsewhere in this guideline. Useful references for the statistical approaches demonstrated in this guideline can be found in Section 17 – References (19, 25-27). Data evaluation for reduced study designs is described in Annex 1 (Reduced Stability Protocol Design) and Section 13 (Data Evaluation).

A2-1.1 Evaluation of Variability for Stability Data in Single-factor, Full Design Studies Using Linear Regression Models

In general, the mathematical relationship between certain drug substance or drug product quantitative quality attributes and time is inferred to be linear as a reasonable approximation in a range of interest. The guideline (refer to Section 13 – Data Evaluation) describes how, for chemical synthetic entities, the available long-term stability data may be extrapolated to establish a shelf life using a decision tree approach. Each primary, production and representative development batch in a formal stability protocol, stored under the long-term conditions, may be evaluated separately and the worst-case batch used to establish the re-test period or shelf life. Combining multiple batches is discussed in Annex 2, Section A2-1.2 - Linear Models Used to Assess Stability Profile and Section 13.2.2 - Combining Batches.

Figure: A2- 1 shows the single batch (single-factor) regression line for assay of a synthetic chemical drug product with upper and lower acceptance criteria of 105 percent and 95 percent of label claim for assay, respectively. From 12 months of long-term data, a shelf life of 24 months can be proposed by extrapolation if no significant trends in accelerated and/or intermediate stability data. In this example, two-sided 95 percent confidence limits for the mean are calculated. The lower confidence limit intersects the lower acceptance criterion at 30 months, while the upper confidence limit does not intersect with the upper acceptance criterion until later. Therefore, the proposed shelf life of 24 months can be supported by the

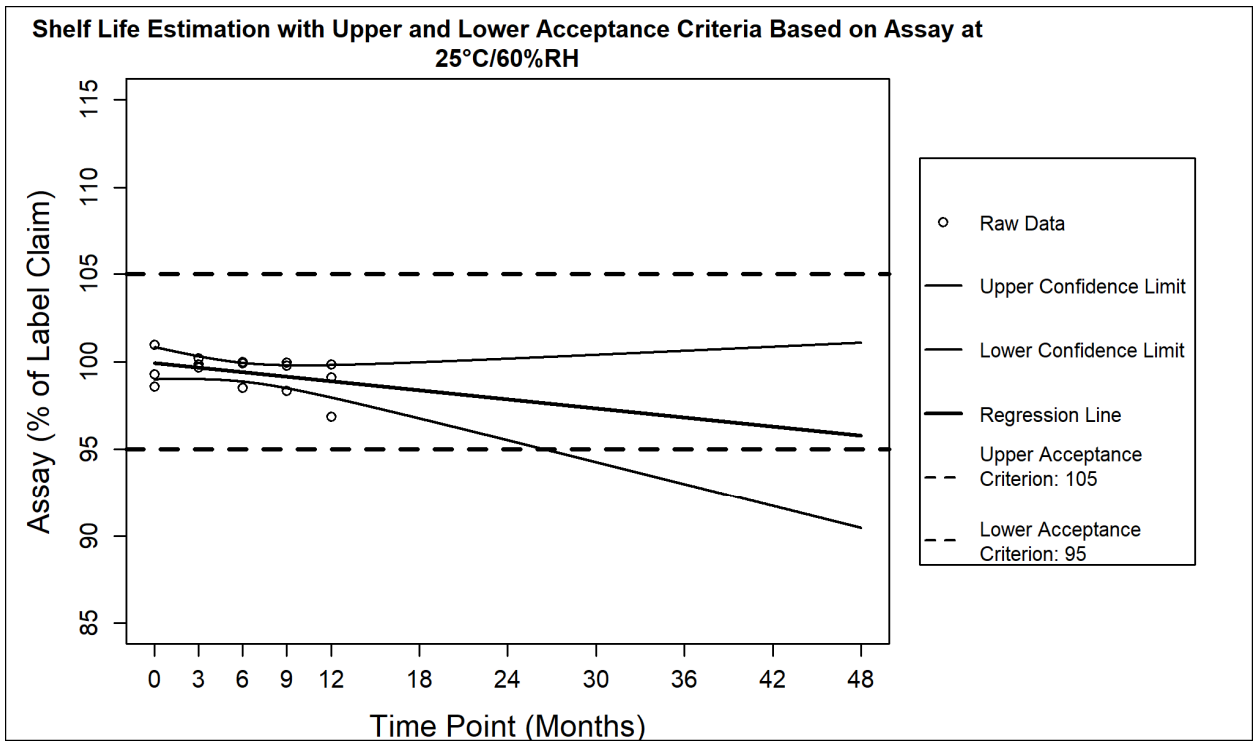
2292 statistical analysis of the assay. A similar approach may be used for an attribute, such as an impurity, that
2293 increases over time and has a one-sided upper 95% confidence limit intersecting the attribute specification
2294 and support the target shelf life (: Shelf Life Estimation with Upper and Lower Acceptance Criteria



2295

2296 Figure: A2- 2). When the above approach is used, the mean value of the quantitative attribute (e.g., assay,
2297 degradation products) can be expected to remain within the acceptance criteria through the end of the re-
2298 test period or shelf life at a confidence level of 95 percent.

2299 **Figure: A2- 1: Shelf Life Estimation with Upper and Lower Acceptance Criteria**



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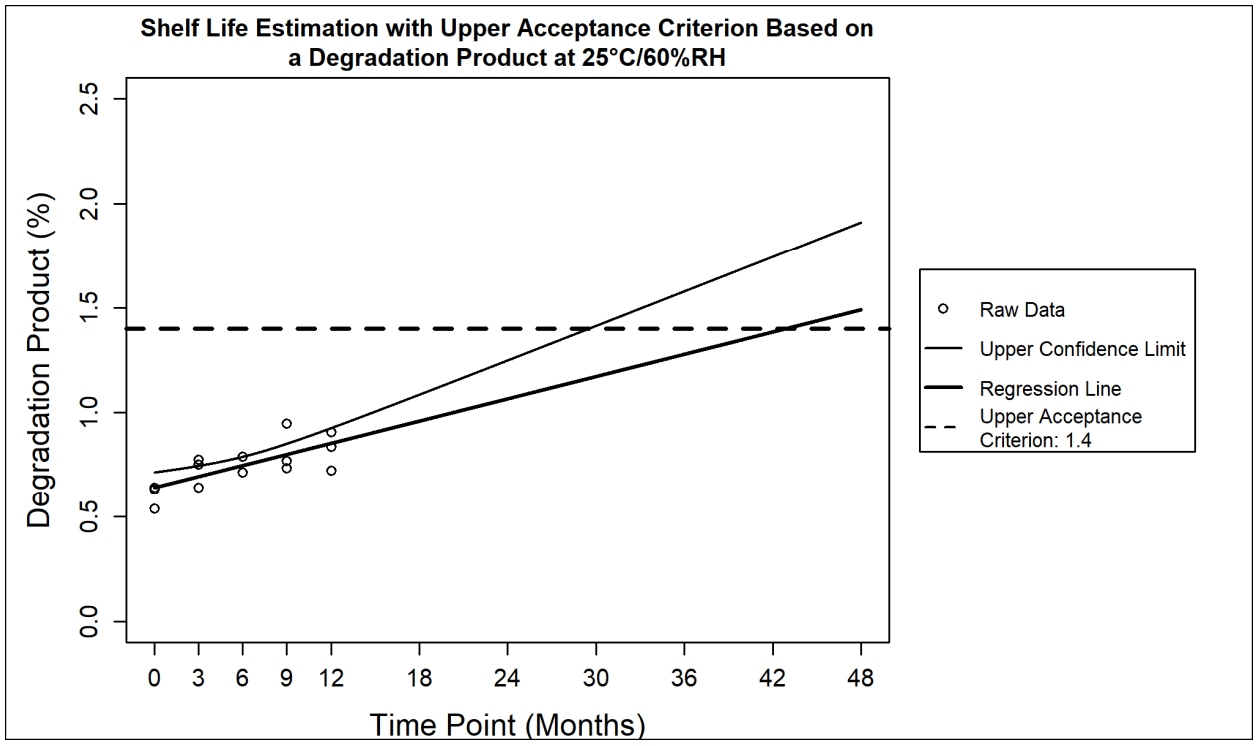
2301 **Figure: A2- 2: Shelf Life Estimation with Upper Acceptance Criterion**



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A2-1.2 Linear Models to Assess Stability Profile Using Multiple Batches

When stability data for more than a single batch are available, the data evaluation may use a linear model to evaluate the attribute stability profile at stated storage conditions and either establish or support a re-test period or shelf life. A linear model (Analysis of Covariance (ANCOVA), fixed effects or mixed effects model) may be applied to stability data, in which, the aim is to generate confidence bounds (or tolerance intervals for mixed effect models) and establish the maximum re-test period or shelf life that may be claimed. The accuracy and precision of the analysis is determined by the number of batches suitable for the analysis, confidence in the uniformity of data, and the number of data points within each time-course study. Applicants are advised that there is inherent risk of inaccurate representation of the stability profiles of manufactured batches dependent on the number of batches used and that batch numbers should be a consideration for study design. The minimum data set is discussed in the guideline (refer to Section 3 – Stability Protocol Design). A confidence interval based approach may be applied to evaluate shelf life when long-term data through shelf life are available (20).

Two model types are outlined below for the linear regression evaluation of stability data to establish re-test period or shelf life, fixed effects and mixed effects models. The models transform according to whether the batches are considered as a fixed (refer to Annex 2-Stability Modelling, Section 1.2.1 – Fixed Effects Model) or random variable (refer to Annex 2, Section 1.2.2 – Mixed Effects Model) and whether the variables are fixed or random. The choice of model generally depends on the number of batches used for the evaluation.

A2-1.2-1 Fixed Effects Model

A Fixed Effects Model may be chosen when limited batches are available, e.g., three primary stability batches. The ANCOVA Fixed Effects Model expresses the attribute value at each timepoint and each batch as a function of the average y-intercept and average slope with their respective variability across the batches. The level of significance for similarity between batches for intercept and slope should be proportionate to the number of batches used in the analysis, where a higher number of batches leads to lower significance level. When only 3 batches are available representative of the production batches, the model may consider batch as a fixed effect rather than as a random variable, with a selected significance level (p-value) for intercept and slope of 0.25. From regression lines, 95% confidence bounds for attributes may be one-sided or two-sided, depending on their acceptance criteria and if the attribute is known to be increasing or decreasing, e.g., a purity attribute typically has a one-sided acceptance criterion, whereas potency, for a biological drug substance or drug product, typically has two-sided acceptance criteria. Increasing the significance level for one-sided confidence intervals may be appropriate.

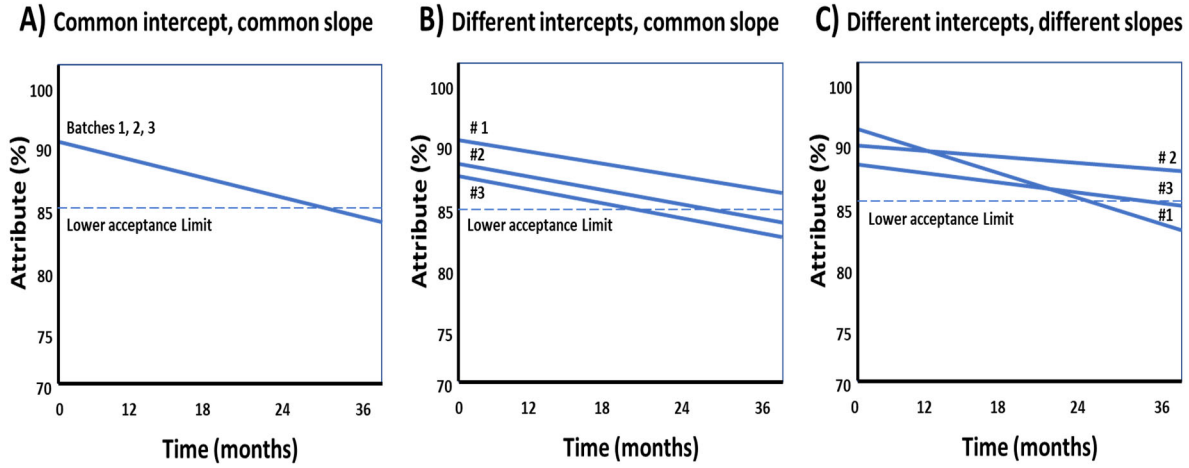
The possible models after sequentially evaluating the significance of slope variability and intercept variability between batches are indicated in Figure 3. There is no option for Different Slopes, Common Intercept because it is not realistic from a practical perspective to have all batches start from the same initial value at time (t)=0, but then have different slopes. When there is a distribution for the attribute at release (time zero), owing to lot-to-lot and assay variability, the model allows for different intercepts between batches.

Scenario A: When the statistical analysis demonstrated no statistically significant differences among slopes and no statistically significant differences among y-intercepts (p-values > 0.25), the batch term is dropped from the model and a common slope/common intercept model is fit to the data, which can be recognised as a simple linear regression model supporting, in this example, a 24 months shelf life based on the confidence bound crossing the shelf life specification acceptance limit at or after the proposed shelf life.

Scenario B: For attributes where the differences between the slopes were not statistically significant (p-value > 0.25), but differences between the y-intercepts were statistically significant (p-value < 0.25), the common slope/different intercepts model was used as the final model. The worst-case batch was identified as described in Figure 3 (batch #3). The shelf life is met if the worst-case batch's confidence bound crosses the shelf life specification acceptance limit at or after the proposed shelf life (e.g., after 18 months).

Scenario C: For attributes where the differences between slopes were statistically significant (p-value <0.25), the different slopes/different intercepts model was used as the final model. The worst-case batch is the one whose confidence bound yields the earliest intersection with shelf life specification acceptance limit (batch #1). The shelf life is claimed if the worst-case batch's 95% confidence bound crosses the shelf life specification acceptance limit at or after the proposed shelf life (e.g., after 24 months).

Figure A2- 3: Potential Final Models After Evaluating Slope and Intercept



The final models per attribute may then be used to predict the mean attribute values and the 95% confidence bound(s), to establish the re-test period or shelf life as no more than the point of intersection of the appropriate upper or lower confidence bound with the attribute specification.

Mixed Effects Model

A mixed effects model may be chosen when five or more batches are available for statistical evaluation so that batch can be treated as a random variable. Batches, in addition to those defined as the primary stability batches, would be deemed as sufficiently representative of the primary batches and future production batches through analytical comparability with differences concluded to not impact the stability profile of the drug substance or drug product. A mixed effects model is recommended when there is risk to batch uniformity (i.e., greater risk of batch to batch variability). If the variance components for the random slope and intercept terms are estimated to be or close to zero (0), applying the fixed effect model can be more appropriate.

The mixed effects model reflects the expectation of random variation among the batches in terms of initial levels and trends over time (i.e., intercepts and slopes for a linear model), and hence the true shelf life is unique to each batch. The larger number of batches provides greater assurance that the inferred stability profile is representative of future batches manufactured using the same process. A tolerance interval-based approach using the linear mixed effects model may be applied to determine an extended shelf life beyond the period covered by long-term data. For instance, the shelf life of the product is determined as the (latest) timepoint where the (95%) the lower confidence limit of the 5th percentile (or the lower limit of the 95%/90% tolerance interval – first percentage refers to population covered, second confidence level) of the

CQA is above acceptance limits. Corresponding tolerance interval-based approaches may be used to extrapolate an extended shelf life beyond the period covered by long-term data from the linear mixed effects model.

A2-2 Enhanced Stability Modelling

This section provides scientific and regulatory considerations for enhanced stability model development, qualification and maintenance over product lifecycle for the purpose of supporting a re-test period or shelf life. Guidance is provided for stability models that may be applied to well-understood drug substances or drug products that have been extensively characterised, including the identification of their relevant degradation pathways. When enhanced stability modelling is used, applicants are encouraged to consult with regulatory authorities to understand submission expectations.

Focus is placed on the design and data evaluation of enhanced stability models that can evaluate and extrapolate linear and non-linear quality attribute changes over time and includes the use of prior knowledge. Linear regression for the extrapolation of stability data and the use of stability data from different batches are discussed in the core guideline (refer to Section 13 – Data Evaluation) and Section 1 of this Annex (refer to Section A2-1 Statistical Evaluation of Stability Data from Single or Multi-factor Study Designs).

A2-2.1 General Principles of Enhanced Stability Modelling

The principles described in the ICH Points to Consider guide to implement ICH Q8/Q9/Q10, apply to stability models that are used to extrapolate re-test period or shelf life. These concepts are expanded in the subsequent sections of this annex. A stability model used to set commercial re-test period or shelf life would be considered a High-Impact Model in accordance with the elements for consideration in model validation, verification and documentation and would be of higher risk, than, for example models used during development studies.

There are many types of stability models available or currently under development and, correspondingly, the tools to evaluate data from such stability models. This annex covers general principles of currently known kinetic, thermo-kinetic and mechanistic models as well as *in silico* or *de novo* computational methods that simulate known attribute stability profiles. This annex does not attempt to be comprehensive in describing all possible stability models or means of model data evaluation that could be considered acceptable when justified. Stability models may be empirical in nature by fitting the available stability data and known variables to derived mathematical relationships that describe how the quality attribute stability

profile changes over time and measured under defined conditions. While enhanced stability models may be used to predict the stability profile at submission, these models should be considered as part of a comprehensive stability program and are not intended to replace long-term stability studies.

An enhanced level of understanding for a drug substance or drug product under development (ICH Q8), which may encompass prior knowledge from drug substance or drug product development studies and information from structurally and functionally related molecules, referred to as "analogous molecules", enables the use of stability models. See Sections 2 (Development Studies under Stress and Forced Conditions) and 3 (Stability Protocol Design) for considerations for prior knowledge. The sum of knowledge of the available stability data including confirmatory data, could support a quantitative prediction model.

There are many situations when a stability model may be applicable, including: setting the re-test period or shelf life and assessing the impact of storage condition excursions or manufacturing changes. A stability model may be applied during drug substance or drug product development, for an initial regulatory submission or as a post-approval, lifecycle management activity. The purpose of the model and the specific context of its use should be clearly stated.

A2-2.2 Model Development

A2-2.2.1 Choice of Model Type

Certain types of stability model are built using data obtained at elevated conditions of temperature and/or humidity. The experimental accelerated conditions may be a selected set of defined parameters that may or may not overlap with the formal accelerated and stressed storage conditions as described in Section 7 - Storage Conditions.

Depending on the underlying principles of the proposed stability modelling methodologies, the product type under consideration and the specific purpose of the model, certain model types may be more appropriate than others. The choice of model could depend on:

- the intended context of use for the model,
- fit of stability data at the recommended storage condition to a kinetic formula,
- thermo-kinetic reactions with the fit of Arrhenius equation or its derivatives to stability data at accelerated temperatures,
- the access to relevant prior knowledge,
- the nature of the shelf life limiting attributes, their criticality ranking, impact on the stability profile

- and known correlations with structure or function of the molecule.

The appropriateness of the selected model for its intended use should be briefly described and justified in the specific context of its proposed use. The model should be described in sufficient detail to understand how it was developed and how the model is used to provide accurate prediction or inference of a quality attribute stability profile.

A biological drug substance or drug product may be less amenable to modelling by the humidity modified Arrhenius equation using accelerated condition data, whereas the temperature/humidity-dependent kinetics for a solid synthetic chemical drug substance or drug product may obey the humidity modified Arrhenius equation for the shelf life limiting attributes. In addition, a model, on a case-by-case basis, may not be appropriate for physical attribute changes.

Enhanced stability models can fall under two broad classes: (1) those that utilise only the product-specific representative batch stability data (long-term and/or accelerated) and (2) those that additionally utilise prior knowledge from analogous-molecules combined with the product-specific information. Prior knowledge may be incorporated into the stability model evaluation in different ways, for example, to establish an acceptable range for the attribute stability profile, or by using Bayesian statistics.

It is recognised that novel model types are likely to emerge in the future (e.g., use of Artificial Intelligence Machine Learning, AI-ML). The principles outlined in this Annex should be generally applicable when developing a novel stability model, though other considerations regarding data requirements may also apply. Early engagement with regulators is recommended in such instances.

2.2.1 Selection of Critical Quality Attributes for Stability Modelling

Those attributes selected for modelling should be chosen according to the purpose of the model and the available stability knowledge. Those attributes not selected for modelling should be justified. The selection of CQAs for modelling follows the same principles described in the core guideline for protocol design and adapted to the purpose of stability model development. The selection of stability-indicating CQAs used in models, from those that define the stability profile (refer to Section 3 – Stability Protocol Design) should be justified and the impact of an attribute (not part of the model) changing unexpectedly should be considered as part of risk management (see Annex 2-Stability Modelling, Section 2.5-Risk Management and Model Lifecycle Considerations).

To establish a re-test period or shelf life, the CQAs that have been identified as those most likely to impact the product shelf life, would be selected for stability modelling, that is, those attributes that are considered

to most likely approach the upper or lower bounds in the attribute specification over the storage period (ICH Q6A and 6B) and are 'shelf life limiting'. The selected quality attributes should be justified and be the focus for developing a stability model.

A2-2.2.2 Selection of Data and Parameters to Construct a Stability Model

The data used to build a stability model are typically based on results from the long-term primary and production stability batches or at accelerated conditions (e.g., elevated temperature and/or humidity). They may also incorporate data from earlier development studies when there is sufficient understanding of comparability between the development and production molecules.

When limited data from the formal stability protocol are available, one may consider leveraging prior knowledge into the evaluation and model building. Prior knowledge from non-product analogous molecules may supplement the product-specific stability data. Models being developed using information from other, related products require access to sufficient prior knowledge that can be justified as transferable to the drug substance or drug product. The prior knowledge molecules that are grouped as a family or class may be justified through an evaluation of relevant characteristics for the differences between the prior knowledge molecule(s) and the drug substance or drug product. These characteristics may include structural modality, stability influencing attributes, manufacturing processes, formulation, container closure, storage conditions, analytical procedures and the available stability data, including degradation profile. Prior knowledge may be used together with primary and production batch data to generate a stability model. Any prior knowledge data from the molecule or analogous molecules should be described and structure-function differences justified, in terms of impact on a stability profile. In addition, similar analytical procedures should be used for the attributes so that the data can be appropriately transferred for inclusion in generating the stability model.

When prior knowledge from analogous molecules is used in a stability model, it is important to identify and address any potential for bias that could result in over-fitting or under-fitting of the model, thereby reducing model accuracy. The management of bias in the model from the datasets used should be described.

The parameters (e.g., reaction rate, order of reaction) used to build a stability model should be chosen to maximise the accuracy of the inferred stability profile, while avoiding over-fitting. When prior knowledge is available, model accuracy may be assessed by using a relevant dataset that is not included in the model design for which the stability profile is known. The development of a stability model may run through several iterations while optimising the parameters to achieve a final, simplest model that provides the best prediction accuracy (least difference between the predicted value and actual experimental value).

A2-2.3 Evaluation of Data for Stability Modelling

The statistical approach and associated statistical parameters used should be clearly described and justified. Stability models define the trends of quality attributes that change over time, based on experimental data that may be linear or non-linear. The statistical approaches for molecule-specific stability data evaluated using linear regression and for the combining of batches for drug substance or drug product are outlined in Section 13 - Data Evaluation of the core guideline and Section 1 of this Annex. The following sections in this Annex provide additional options when using the enhanced stability models for the purpose of extrapolating the stability profile past the available data at the recommended storage conditions. The data distribution over time is typically characterised using justified statistical intervals to ensure that a defined proportion of the data lies within or that future data will lie within the interval, as appropriate for the model and statistical interval chosen.

Most current enhanced stability models start with an empirical approach with the experimental stability data being compared to a mathematical or kinetic function of time. When an empirical model is used and the available stability data are being compared to the model, a demonstration of goodness of fit should be performed using appropriate statistical tools to avoid overfitting the kinetic function to the data when the model incorporates the variability and thereby reducing the accuracy of prediction.

It is important that the accuracy of the model to infer or predict the stability profile, past the last time point of the available data, is demonstrated using appropriate statistical tools (19-27). For example, by applying the model to a known, full stability data set, for which the last timepoint result(s) has not been included, the value for that last timepoints may be predicted. The predicted value can then be compared to the known, experimentally derived value as a measure of accuracy. For quality attributes with high variability, other statistical methods of model validation should be considered because demonstration of the model's accuracy for any single timepoint may not be sufficient.

Prior knowledge data may be evaluated using Bayesian statistics as an alternative to conventional Frequentist statistics and can allow for prediction of drug substance or drug product stability data over time, past the point of available long-term condition data. The Bayesian method derives a posterior distribution for the parameters of interest by combining the likelihood distributions for the observed data with the prior knowledge. The method for derivation of the prior distribution should be justified by the applicant. The general principles outlined in this Annex for a stability model would apply to models using a Bayesian approach including verification and validation to demonstrate that the model and data used are fit for the intended purpose.

While enhanced modelling strategies are not currently associated with an upper limit for shelf life and re-test period prediction, applicants should provide risk-based and scientifically justified duration for the proposed shelf life or re-test period using enhanced approaches. When utilising enhanced stability modelling to support a shelf life or re-test period, the extent of prediction should be based on scientific understanding, risk assessment (including totality of available long-term and supportive data), prior knowledge (e.g., representative batches out to the proposed shelf life), considerations of the limits discussed in Section 13 - Data Evaluation, container closure limitations, feedback from model lifecycle considerations (e.g., emerging confirmatory data) and statistical design.

A2-2.4 Model Validation and Verification

A stability model should be shown to be suitable for its intended purpose. This may be demonstrated through validation and verification procedures, for which the methodology would depend on the purpose and type of model. A comprehensive approach to model verification and validation should include discussion with experts in both analytical and statistical approaches. Model predictions may be validated by using data from earlier development studies, provided comparability has been demonstrated and the batches are considered representative of the commercial material (refer to Section 4- Selection of Batches). When a model uses accelerated condition data and the degradation kinetics obey a modified Arrhenius equation, the model may be considered as verified by fit to the modified Arrhenius equation at different storage conditions.

Stability models are not intended to replace long-term data through the proposed re-test period or shelf life, which should be performed in addition to the model. Data should be continually obtained and evaluated, as confirmatory or ongoing verification, to assess whether the model predictions are still reliable. Models that are built using accelerated condition data may include the available long-term stability data as part of the model verification.

A2-2.5 Risk Management and Model Lifecycle Considerations

Any stability model that infers or predicts a stability profile beyond the available drug substance or drug product data, incurs an inherent risk. A description of risk management should be provided in the regulatory submission that introduces an enhanced stability model used for setting re-test period or shelf life. The risks in using a stability model should be identified using risk management methodologies (ICH Q9) and, when applicable, appropriate mitigation strategies should be in place to reduce those risks through verification and validation activities. The resulting risk of using the stability model should be as low as possible. Use of stability models is intended for drug substances and drug products that are well understood,

for which the quality attributes would be known, and their corresponding criticality and residual risks evaluated to ensure patient safety. The stability-indicating attributes are also selected, and the stability profile defined. Particular note should be taken in discussing risk presented by any use of "analogous molecules" that refers to differences between molecules that may impact their stability profile and the extent that the knowledge is transferable for use in the stability model.

A stability model, depending on the model type and intended purpose, may require updating through drug substance and drug product lifecycle. The need to update a model should be evaluated as part of risk management. The risk assessment outcomes (from formal or informal risk management as described in ICH Q9) should also be reviewed as new data are obtained through the period that the stability model is in use. Generally, when a model is used once to establish a re-test period or shelf life it would not be necessary to continuously update the model during lifecycle management as long as new long-term stability data are obtained that support the identified attribute trend. The post-approval and ongoing monitoring/trending of new drug substance or drug product stability data should be managed by the manufacturer's PQS (Pharmaceutical Quality System). The PQS should be capable of detecting and managing any unexpected changes in stability trend and out of specification results with appropriate corrective action and preventive actions (CAPA) as described in ICH Q10, relevant to any stability model being used to establish re-test period or shelf life. Should an unexpected change in trend be confirmed with potential for the attribute to exceed acceptance criteria and impact the re-test period or shelf life, the model and its use should be reassessed.

Annex 3 Stability of Advanced Therapy Medicinal Products (ATMPs)

A3-1 INTRODUCTION

Advanced therapy medicinal products (ATMPs) are a diverse category of innovative and complex biological products which includes somatic cell therapy, gene therapies and tissue-engineered products. ATMPs have several unique characteristics that should be reflected in the design and execution of the stability program. In some circumstances, the mechanism of action may be complex with multiple targets and potentially multiple modes of action and, as such, the critical quality attributes are not always fully understood. Owing to their complex degradation properties, accelerated stability testing conditions may not be predictive of the actual degradation profiles during storage. However, if accelerated studies can be utilised to support knowledge of the degradation profile and/or stability profile, then data and justification can be provided. The small batch size for some patient-specific ATMPs can severely limit the availability of material for stability testing. ATMPs that are designed for small patient populations may be manufactured in small batch sizes or a single batch that may even be sufficient for the entire clinical study, leading to challenges in conducting stability studies using multiple production batches. ATMPs are a class of therapeutics, which may have limited prior knowledge available to support model-based approaches to the stability assessment. In general, the shelf life for drug substance, intermediate, and/or drug product should be based on real-time stability studies.

This annex provides recommendations for designing stability studies for ATMPs. When a topic is not included in the Annex, the reader is referred to the core guidance for stability principles that are considered generally relevant to ATMPs. The basic elements of the information detailed in Section 3 - Stability Protocol Design through to Section 14 - Labelling should serve as the basis for designing a stability program for ATMPs. For example, where an in-use period is warranted, the applicant should refer to Section 11 - In-Use Stability for general information on the principles, with the caveat that not all information in these sections may be directly relevant to ATMPs.

A3-2 SCOPE

The recommendations in this annex apply to the assessment of stability considerations for drug substance, intermediates, and the drug products of ATMPs as appropriate depending on the product and the manufacturing process. This annex also addresses the stability considerations for starting materials (e.g., viral banks/viral seed stock). Stability considerations for reference materials used in the assessment of ATMPs are consistent with those for reference materials for other biologicals and is discussed under Section

12.1.2 - Consideration for Biological Reference Materials, of the core guidance. The document covers the generation and submission of stability data for products containing biological active substances such as autologous and allogeneic cell-based products (e.g., mesenchymal stromal cells (MSCs), Islet cells, T-cells, NK cells), xenotransplantation products (e.g., animal derived cell products), gene therapy products that are directly administered to humans (e.g., genetically modified cells, recombinant nucleic acids, viral and genetically modified bacterial vectors), oncolytic products, genome editing products and tissue engineered products.

This Annex is applicable to vectors that are administered directly as a drug product or used ex vivo to modify cells (e.g., retroviruses, adeno associated viral and other nucleic acid-based vectors) and viral banks used in the manufacture of viral and bacterial vectors.

Due to the diversity of ATMP products, the stability program should be based on process and product knowledge. The recommendations in this annex will highlight specific differences in product types, but any stability plan should consider the type of ATMP product and its manufacturing process. For example, the primary stability protocol for a vector-based gene therapy for treating larger patient populations may be different from a patient-specific cell-based therapy (i.e., personalised cellular therapies).

A3-3 STABILITY STUDY DESIGN

As outlined in the core guideline, stability studies should be established based on an understanding of the product's CQAs. ATMP stability study design should be based on process and product knowledge of the specific product type and manufacturing process. Stability testing frequency should follow the recommended testing frequency as detailed in Section 6 – Testing Frequency. When the patient specific ATMPs are stored or when the available product lot has a limited quantity, a risk-based approach to testing frequency is recommended and should be justified based on available developmental data and prior knowledge. Stability studies for ATMPs may be performed using container closure system differing from the commercial system, when justified and supported by data showing suitability of the alternative container closure system. Shipping stability studies for ATMPs should generally follow the principles described in the core guidance. Shipping stability studies for cell based ATMPs should also include tests to evaluate the effect of physical forces exerted during shipping.

The applicant is encouraged to use a risk-based approach to the design of the stability study. Where a risk-based approach is employed, the risk assessment and supporting justification should be provided.

A1-3.1 Selection of Analytical Procedures and Acceptance Criteria

Selection of analytical procedures and acceptance criteria are detailed in the core guideline (refer to Section 3.4 - Specification). Uncertainty surrounding stability CQAs due to high assay variability may be mitigated by performing orthogonal assays, where for a given CQA, orthogonal assays may provide greater confidence in the stability trends over time. Potency is a critical quality attribute for determining stability of ATMPs. However, assessing potency of some ATMPs may be challenging and complex due to incomplete knowledge of the mechanism of action of the product, absence of suitable analytical procedures to accurately predict the product function, the inherent variability in patient-specific products, and due to the complex modes of action of the ATMP to exert a given result. Therefore, determining the change in potency during storage should be performed through a suitable assurance of the intended biological effect. The capability of the chosen potency assay to detect subpotent or degraded product should be justified and an evaluation of the degradation profile and its impact on potency provided. When one assay is not sufficient to fully evaluate all the different product functions, multiple assays may be used to assess potency. For cell-based products, this may be evaluated through tests such as cell viability assays, immunochemistry and immunoassays for cell surface markers, and assays that evaluate function (potency). For gene therapy products, this may be evaluated through tests such as transduction, infectivity, gene expression, and/or activity of the expressed product.

The purity of the ATMP should be assessed to ensure that storage period and conditions do not lead to an increase in the levels of impurities beyond the demonstrated acceptable range. Impurities in ATMPs result from either the manufacturing process or are product related, where the latter may include for instance the following impurities: dead cells, empty viral particles, or degraded products. While process-related impurities are controlled during the manufacturing process, storage conditions and duration of storage may lead to an increase in the product-related impurities. For this reason, a quantitative enumeration of the levels of product-related impurities in an ATMP should be assessed and the acceptable stability limits should be justified. Stability attributes related to product impurities should be based on a risk assessment at various manufacturing and storage steps (e.g., freeze-thaw step). Based on the risk, measurement of representative characteristics of the degraded/product derived material may be sufficient to assess stability, when performed in combination with other product CQAs.

In addition to the general considerations for assessing stability of ATMPs, the following are examples for product-specific stability considerations that should be evaluated as a part of the stability assessment (additional product-specific parameters may also be required to assess stability):

- For live cell-based products that are stored frozen, it is important to measure viability of cells after they are thawed as part of the stability studies. The impact of changes in cell viability and cell concentration should be considered for subsequent processing (for intermediates) or dosing (for final product).

- For virus-based products, product CQAs such as changes to total particle number, genome copy number, infectious particle number and viral genome titre should be included in the stability studies.
- For viral therapy vectors that are used to further modify cells ex vivo, vector integrity, potency and strength are stability-indicating CQAs that should normally be included in stability studies.
- For bacteria-based products, the viability, bacteria count, plasmid copy number (if applicable) should be considered.
- For DNA or RNA based products, stability determination may also include an assessment of structural integrity and quantity in addition to other purity assessments.
- For Tissue Engineered products physicochemical and functional critical quality attributes should be evaluated as a part of the stability studies. The product's structural stability may be evaluated through tests such as measurement of size and shape, and assessment of structural integrity. In the case of products formulated with carrier or support materials, the stability of the complex formed with the drug substance should be studied.

Acceptance criteria should be justified considering the data from material used in preclinical and clinical studies. For substances that cannot be properly characterised or products for which an exact analysis of the stability-indicating CQAs cannot be determined through routine analytical procedures, the applicant should propose and justify alternative testing procedures. The attributes tested for batch release may not be entirely suitable for stability determination for some ATMPs (e.g., definition of mature and immature dendritic cells based on the surface expression of markers such as CD80, CD86, CD83, and MHC II; percent (%) transduced products in case of an *ex vivo* modified cellular product; virus phenotype and genetic identity of virus). Acceptance criteria for acceptable impurities should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies, and batches that did not adversely impact safety or potency should be used to set acceptance limits for impurities. When justified, shelf life specifications may differ from the release specification.

A1-3.2 Selection of Study Conditions

Recommendations around the selection of study conditions are outlined in the core guideline (refer to Section 3 – Stability Protocol Design through Section 7 – Storage Conditions). It is expected that the stability studies for ATMPs include real-time storage and in-use period conditions. Generally, accelerated or stress testing may not provide direct information to support shelf life, however testing under accelerated and stressed conditions are recommended for ATMPs. Accelerated studies may be utilised to gain knowledge of the stability profile. Testing under these conditions help in the determination of the extent of temperature deviations that can be tolerated while the harsher stress conditions may provide information on the degradation profile of the product. Accelerated or forced degradation studies can also be useful to demonstrate the stability-indicating nature of assays and their corresponding levels of sensitivity. The accelerated conditions defined in Section 7 - Storage Conditions of the core guideline may not be directly applicable for ATMPs, and the accelerated and stressed conditions should be carefully selected based on a risk assessment and worst-case conditions relevant to ATMP's handling and storage.

A1-3.3 Selection of Batches

Recommendations around the selection of batches are outlined in the core guideline. Generally, stability data from 3 primary batches are recommended to support the proposed shelf life of ATMPs, however on the basis of risk evaluation alternative number of stability batches may be justified. The risk to an accurate determination of predicted shelf life of an ATMP will depend on various factors including the assay limitations and variabilities in and the quality of starting materials. The shelf life of ATMPs should generally be justified based on long-term stability data through the proposed shelf life. In some instances, a stability profile based on prior knowledge from analogous products (refer to Annex 2-Stability Modelling) may provide additional supporting stability data. As described in the core guideline Section 4.1 - Considerations for Selection of Primary Stability Batches, the manufacturing scale of the primary stability batches for ATMPs may differ from that of the production batch, unless the scale change represents a significant risk to stability. Primary stability batches may be clinical batches not at production scale, provided appropriate comparability has been demonstrated to production batches. When primary batches are not production scale batches, a post-approval commitment may be required to confirm the stability.

Stability of patient-specific cellular ATMPs should be obtained from patient derived materials. However, this may not always be feasible due to limited availability (e.g., autologous CAR-T cells), and when justified, stability data from representative healthy donor derived materials along with stability data from patient-derived material may be acceptable. When patient derived material is only available in limited

quantities to perform the recommended stability studies as per the stability protocol, the principles of bracketing (refer to Annex 1 - Reduced Stability Protocol Design) may be applied to ATMPs. Stability-indicating CQAs that are assessed to determine stability will depend on the drug product and should be justified. Stability of cryopreserved cells used as cell substrates for the manufacture of ATMPs may apply the principle of modelling based on prior knowledge (e.g., cell type, formulation, container, cell density) to set initial shelf life beyond long-term data at submission.

ATMPs may differ in the standard manufacturing process flow without having distinct bulk drug substance batches and manufactured in one uninterrupted stream with no distinct drug substance storage step. Under such circumstances, there would not be a need to evaluate the storage period of a drug substance. Examples of this type of manufacturing include a number of cell-based products that are continuously cultured, purified, formulated and stored (or administered fresh) as the final ready-to-use drug product.

For ATMPs that have a distinct drug substance stage, the date of manufacturing of the drug substance and the date of manufacturing of the drug product may be two separate dates and the duration of storage of the drug substance prior to it being processed into the final drug product may influence the storage period of the drug product. If this is the case, a risk assessment should be performed to determine if the stability assessments should also take into consideration the cumulative storage period of the drug substance and drug product.

When the manufacturing process includes a short hold time, a risk assessment to determine the need and extent of hold time stability studies should be assessed and justified. Some ATMP manufacturing process may include a freezing step (e.g., short term storage of cells prior to further processing). In such instances, the stability of the stored intermediate should be evaluated upon thaw.

A3-4 STARTING MATERIALS AND STABILITY

The protocol should take into consideration that stability of ATMPs may be affected by the quality of starting materials and viral vectors, and stability assessment should consider the impact of starting materials for cell therapy products (e.g., allogenic, autologous cells), transport, storage steps in the manufacturing process, and their short or long-term storage conditions (e.g., short-term cell storage versus long-term cryopreservation). The stability of cellular starting materials (e.g., donor cells) should be assessed during their storage and shipping. In general, assessment of stability of cellular starting materials during their storage and shipping should follow the recommendations detailed in this guideline for cell based ATMPs and should follow a risk based approach to determining their stability. Stability of starting materials used

to manufacture gene therapy vectors (e.g., plasmids, virus banks used to make vectors) should also be controlled.

Viral vectors that are used to modify cells ex vivo to make ATMPs (e.g., retrovirus, lentivirus) are normally manufactured in bulk, purified and adjusted for a desired concentration and stored frozen until use. Stored viral vectors should be assessed for stability related CQAs, such as vector integrity, strength (e.g., infectious titre, transducing titre, genomic titre and viral particle count), product related impurity profile, ratio of empty to full particles (if applicable), activity (e.g., gene expression), and sterility (or container closure integrity testing). When the viral vectors are stored at varying concentrations, stability of the viral vectors at each individual concentration should be assessed, unless bracketing is justified (refer to Annex 1-Reduced Stability Protocol Design).

A3-4.1 Cell and Viral Banks

The stability of cell banks under defined storage conditions should be generated to verify that the thawed cells have survived the preservation process and retain their CQAs, consistent with the recommendations outlined in ICH Q5D. A stability protocol for monitoring of banked cells should be provided in the submission. Stability-indicating CQAs that are assessed to determine stability should be justified.

Stability of viral banks that are either used in the production of viral drug products for direct administration or for viral vectors used in the production of *in vitro* modification of cells should be evaluated for stability.

The quality of the viral bank should be well established and would typically include an evaluation of its stability-indicating CQAs. When establishing the stability period of viral banks, virus stability may be demonstrated in some cases through assessing the quality attributes of the drug substance, manufactured from the stored material at the end of the viral bank's shelf life. The stability of the established master viral banks (also referred to as viral seed stock in some regions) and working viral banks should be evaluated periodically per a stability protocol. The stability protocol should describe and justify the test parameters and stability acceptance criteria which should be based on its intended use. Potency may also be a stability-indicating CQA, depending on the intended use of the viral bank (e.g., when used to manufacture a viral drug product). Depending on the intended use of the viral bank (e.g., when used to manufacture a viral drug product), infectious titre may also be a stability-indicating CQA and should be included as a part of viral bank's stability assessments.

A3-5 ESTABLISHMENT OF SHELF LIFE

The shelf life of ATMPs may not be accurately predicted from accelerated stability studies, as their behaviour can vary considerably based on the temperature and related changes in the storage medium. When the accelerated stability studies only provide a limited information, due to differences in degradation profile, stability studies designed to support product stability should be performed in real time, under the intended storage conditions. When sufficient real-time stability data from the production lot is not available for ATMPs, stability data from developmental batches and prior knowledge from similar products may be used as supporting data to justify setting initial stability period, with a concurrent testing strategy built into the stability testing protocol. The use of prior knowledge to support shelf life determination of an ATMP should be discussed with regulatory authorities as appropriate.

A minimum of 6 months stability data should be included at the time of submission. The shelf life may be extended beyond the initial 6-month period when additional stability data becomes available. For drug products with storage periods of less than 6 months, the minimum amount of stability data in the initial regulatory submission should cover the intended shelf life.

ATMPs that have a storage period at the drug substance stage and at the drug product stage should be assessed for stability under the stability protocol as detailed in Section 3 - Stability Protocol Design of the core guidance. When intermediates used in the manufacture of cellular products and viral vectors are stored, they should also be assessed for their stability under a pre-specified stability program and a shelf life established based on real-time stability information.