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ICH HARMONISED GUIDELINE

STABILITY TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q1

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ICH Q1

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ICH HARMONISED GUIDELINE

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1 INTRODUCTION

1.1 Objective

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 this guideline as regulatory submissions. ICH Q1 is a consolidated revision that supersedes the ICH Q1A–F and ICH Q5C guidelines and provides additional guidance on principles relating to stability.

1.2 Scope

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 conjugates).
- Vaccines, allergenic products, and adjuvants.
- Autologous and allogeneic cell-based substances, including those which may be genetically modified *ex vivo* and tissue engineered products (for supplemental guidance, 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 (for supplemental guidance, refer to *Annex 3 – Stability of Advanced Therapy Medicinal Products [ATMPs]*).

- The drug constituent part and drug product related performance characteristics of a combination of a drug product with a medical device, also referred to as a drug-device combination product (integral or co-packaged).
- Co-packaged solvents/diluents.
- Other naturally occurring substances that are regulated as drug products.
- Non-radioactive kits and non-radioactive precursors of radiopharmaceutical drugs.

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 (e.g., new drug delivery systems, new dosage forms, different administration routes), and abbreviated or abridged submissions (e.g., generics and biosimilars).

The principles outlined in this guideline are also applicable to support post-approval changes 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 proportionately to increasing levels of product and process understanding during pharmaceutical development.

Data from development batches that meet primary stability requirements may be used to support a regulatory submission and for product lifecycle management.

The guideline is not applicable to device constituent parts 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 relevant environmental and physical factors such as temperature, humidity, light, or agitation. This ensures that the drug substance and drug product maintain their quality throughout the shelf life. 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 may also be referred to as a dating period or an expiration 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 ICH Q14, through increased understanding of critical quality attributes (CQAs), are applicable to the design of an overall stability strategy.

The guideline outlines a standard stability data package for drug substances and drug products and provides guidance on alternative and scientifically justified approaches that encompass the different situations that may be encountered due to specific scientific considerations and characteristics of the data being evaluated. Alternative approaches should be justified and supported by science- and risk-based principles (e.g., as described in ICH Q8–Q11) for drug substances and drug products, leveraging quality risk management principles, pharmaceutical development data (e.g., as discussed in *Section 2 – Development Stability Studies Under Stress and Forced Degradation 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.

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

Unless otherwise specified, the recommendations described in this guideline apply to both the drug substance and the drug product. 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-derived products, and conjugated products, the recommendations for synthetics and biologicals would apply, as appropriate, based on the characteristics of the molecule.
- Where “products” is mentioned by itself in this guideline, this is to be interpreted as “drug substances and drug products”.
- Recommendations for 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 climatic zones

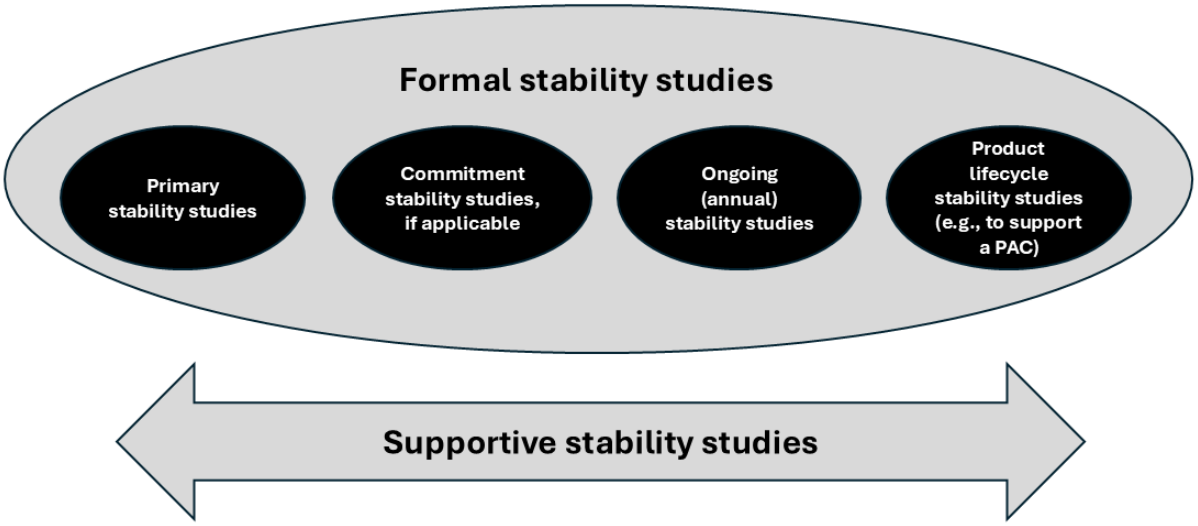
I, II, III, IVa, and IVb (18, 19). These zones are distinguished by their characteristic prevalent annual climatic conditions based on the concept originally described by W. Grimm (20, 21), updated in W. Grimm (22), and adopted under WHO Technical Reports (18, 19). This guideline addresses all climatic 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 (e.g., an antibody prior to conjugation or a spray-dried dispersion), a holding time may be established, or it may be appropriate to establish a re-test period or shelf life in accordance with the applicable sections of this guideline.
- The concept of a "representative batch" 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 recommendations may be applicable to reference materials as well as adjuvants, novel excipients, or certain other excipients 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/adjuvants should follow the considerations applicable to 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.
- The Glossary defines several terms for the purpose of this guideline.

- 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 stability protocol design; Annex 2 provides guidance on stability modelling; and Annex 3 provides additional considerations for stability of Advanced Therapy Medicinal Products (ATMPs).
- This guideline does not specify filing mechanisms or regional requirements.

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

Figure 1: Stability study types



PAC = post-approval change(s)

Formal stability studies are primary, commitment, ongoing, or product lifecycle stability studies conducted under accelerated, intermediate, or long-term storage conditions 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: 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. Guidance is provided on studies that inform stability knowledge and product understanding (refer to *Section 2 – Development Stability Studies Under Stress and Forced Degradation Conditions*). These development studies are introduced in Section 2 because some of this information is utilised to develop the primary stability protocol and in the validation of stability-indicating analytical procedures.

The guideline discusses strategies for protocol design within *Section 3 – Protocol Design for Formal Stability Studies* 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 post-approval changes [PAC]). The applicant should consider all available stability knowledge when designing stability protocols and defining information for inclusion in the product labelling (e.g., storage statements). This includes considerations of the impact of holding times, 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 (refer to *Section 3.7 – Risk Management*). A risk-based approach should be considered to ensure drug product quality throughout storage and use.

2 DEVELOPMENT STABILITY STUDIES UNDER STRESS AND FORCED DEGRADATION CONDITIONS

Development stability studies, such as those under stress and forced degradation conditions, 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 14.1 – 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 – Protocol Design for Formal Stability Studies* and *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management*). In the context of generating product knowledge, studies may be performed under accelerated, stress, and/or forced degradation 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 and physical 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 period, or shelf life determination, and evaluate the impact of excursions outside the labelled storage conditions. Further guidance regarding accelerated testing is described in *Section 3 – Protocol Design for Formal Stability Studies* to *Section 7 – Storage Conditions*.

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

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 are 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.

2.1 Development Studies Under Stress Conditions

Studies under stress conditions can contribute to product knowledge and the data gathered from these studies can be useful in addressing the impact of 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/or freeze-thaw studies, as appropriate. For synthetic chemical entities, these studies may be conducted on one batch of the drug product, and where relevant, on one batch of the drug substance directly exposed or in a container closure system, as applicable. For biologicals, at a minimum, stress studies should 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. The number of batches used should be justified based on the purposes of the stress studies. For certain biological products with greater variability, such as plasma-derived proteins, these studies may require additional batches to account for the inherent variability.

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 the product, and develop and confirm the stability-indicating nature of the analytical procedures (refer to ICH Q2 and ICH Q14). It is acceptable to leverage product knowledge when data are available on identified degradation products and pathways, including scientific literature.

For drug substances, the forced degradation assessment 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 and chemical modification across a range of pH values. Also, a combination of forced degradation conditions may be appropriate to test under certain circumstances (e.g., agitation and heat).

For drug products, testing should include the effect of temperature, humidity (e.g., 75% RH or greater), where appropriate, and light. Additional forced degradation conditions for specific types of products and dosage forms may be appropriate.

For synthetics, it is recommended to assess forced degradation conditions on a single batch of the drug substance and on a single batch of exposed drug product.

For biologicals, the guidance provided may be applied to either a single batch of drug substance or drug product, depending on the purpose of the study. For certain biological products with greater variability, such as plasma-derived proteins, these studies may require additional batches to account for the inherent variability.

The forced photodegradation conditions 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 that are more extreme than the light conditions utilised in confirmatory studies (refer to *Section 8.4 – Radiation Source and Light Exposure*).

With forced degradation studies, the conditions and duration may need to be varied depending on the sensitivity of the product. For development studies 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 products, 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 stress conditions and/or forced degradation conditions, samples should typically 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 for detecting any evidence of change. Changes in attributes that are unlikely to occur under normal storage conditions may occur under stress or forced 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 – Protocol Design for Formal Stability Studies*).

Although development stability studies are not part of the formal stability studies, results from these studies are an integral part of the information provided to regulatory authorities to support different aspects of product quality (e.g., analytical procedure validation, product characterisation, specifications, or packaging considerations). Data from development studies under stress and forced degradation conditions should be included in regulatory submissions if they support a claim on the product labelling or, as appropriate, to support the understanding of degradation pathways and the stability-indicating nature of the analytical procedures.

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* to *Section 7 – Storage Conditions* to establish a formal stability study protocol.

Where noted, these sections provide specific guidance for establishing a primary stability study 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 Lifecycle Management* and *Annex 1 – Reduced Stability Protocol Design*, as appropriate.

3.1 General Principles

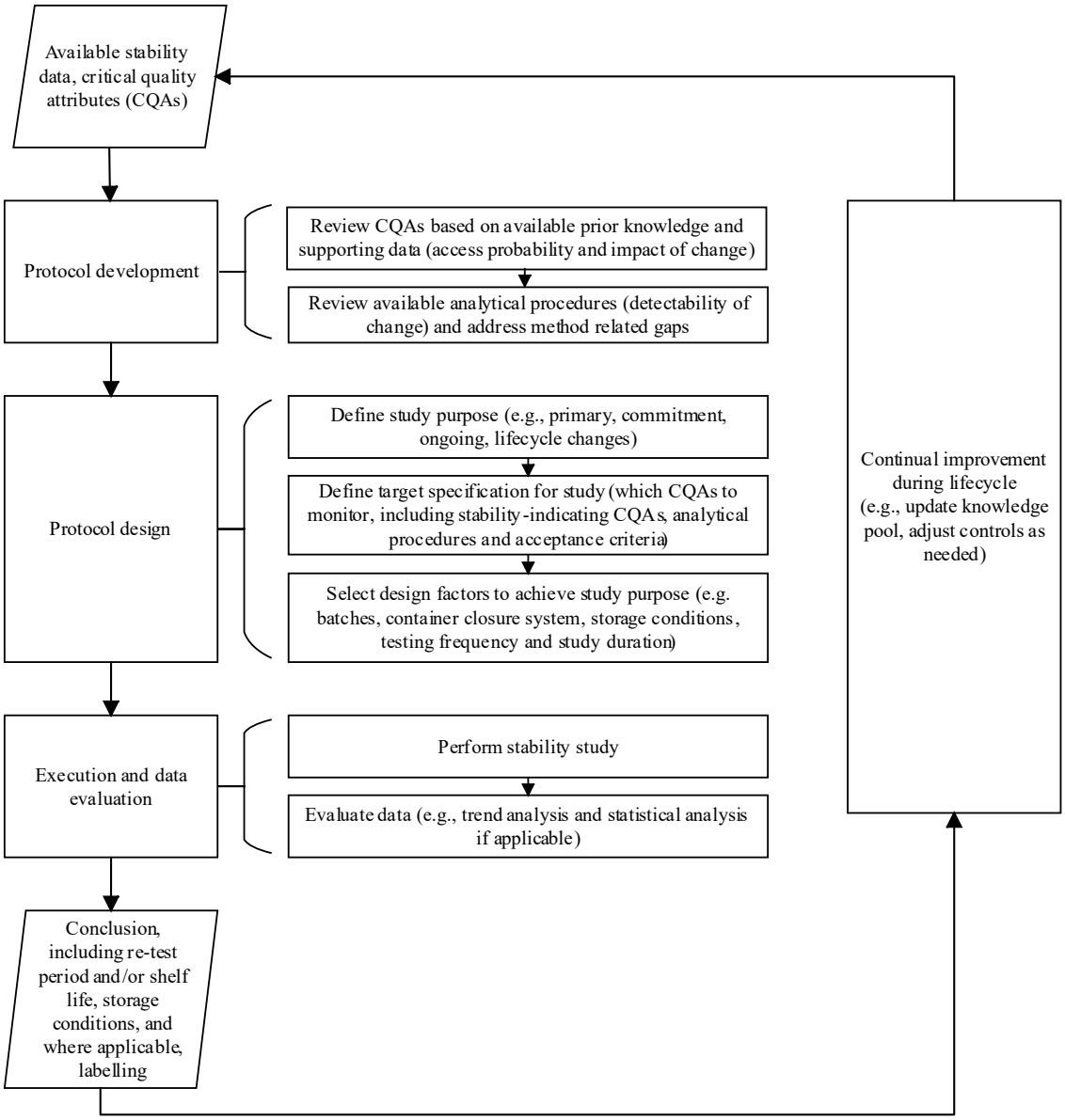
The stability protocol(s) incorporate all necessary information to establish or confirm the stability of the drug substance or drug product under the recommended storage conditions and container closure system throughout the re-test period or shelf life. This includes consideration of data from primary stability studies and supporting data to justify long-term storage, short-term storage, excursions, and in-use conditions, as applicable. Summaries of the stability protocol(s) should be provided in a regulatory submission when a re-test period or shelf life is to be established or confirmed.

An illustration of the general process for the development, design, and execution of a stability protocol is shown in Figure 2, Section 3.1. The "available stability data" in the figure refers to knowledge gained from long-term and accelerated stability studies conducted earlier in development and from the development studies discussed in *Section 2 – Development Stability Studies Under Stress and Forced Degradation Conditions*. 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.

Using this information, the applicant can design a protocol that supports the formal stability studies, in accordance with *Section 3.3 – Critical Quality Attributes (CQAs)* and *Section 3.4 – Specifications*. Stability studies should include testing of those attributes that are susceptible to change during storage and can potentially influence quality, safety, and efficacy. In addition, other CQAs may also need to be monitored during stability studies (refer to *Section 3.3.2 – Other Critical Quality Attributes (CQAs)*.

The stability protocol designs may be optimised throughout the lifecycle of the product, as knowledge is gained and new data become available. Changes to the stability protocol to extend a re-test period or shelf life should be managed in accordance with *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management*.

Figure 2: General process flow for the development, design, and execution of a stability protocol



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

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

A full design stability protocol includes at least 3 representative batches of the drug substance or at least 3 representative batches of each strength of the drug product, covering the proposed container closure systems, so that every combination of all design factors is 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/or Shelf Life According to the Standard Approach

The stability package provided in the regulatory submission should be sufficient to support the proposed re-test period or shelf life and storage conditions. This section provides guidance on establishing the re-test period, shelf life and storage conditions using data from the primary stability study, which is considered the standard approach. The recommendations provided in Table 1, Section 3.2.1 for synthetics and Table 2, Section 3.2.2 for biologicals establish an appropriate minimum dataset at the time of the initial regulatory submission to assign a re-test period and/or shelf life, in accordance with *Section 13 – Data Evaluation*. 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 based on the product-specific risks and in accordance with *Section 4 – Selection of Batches* and *Section 6 – Testing Frequency*.

Alternative approaches to the principles and practices described in this section may be acceptable if they are supported by adequate justification, including enhanced product and manufacturing process understanding from prior knowledge in accordance with ICH Q8–Q11 and stability modelling as discussed in *Annex 2 – Stability Modelling*.

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

The long-term study included in the stability protocol should, at a minimum, ensure that testing continues for the duration of the proposed re-test period or shelf life. Refer to *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management* for guidance on establishing stability commitments to be continued after marketing authorisation.

3.2.1 Stability Data to Support the Initial Re-test Period and Shelf Life for Synthetics

The recommended stability data for the standard approach at submission for synthetics are described in Table 1, Section 3.2.1 and include data generated under long-term storage and accelerated storage conditions for primary batches. Data from the accelerated storage condition are needed to support the proposed shelf life and can enable extrapolation in accordance with *Section 13.3.1 – Extrapolation for Synthetic Chemical Entities*.

For new synthetic chemical entity drug substances and/or drug products for which a new drug regulatory submission is necessary, data from 12 months of long-term and 6 months of accelerated stability studies from 3 primary batches should be provided to support the proposed re-test period or shelf life. In principle, stability protocols for new dosage forms and new strengths/concentrations should follow the guidance for new drug submissions. 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 15.4 – Stability Studies to Support New Dosage Forms and New Strengths/Concentrations*).

For existing synthetic chemical entity drug substances and/or drug products for which an abbreviated/abridged regulatory submission is required, a reduced dataset at submission time is acceptable: 6 months of long-term and 6 months of accelerated stability studies from 3 primary batches. Based on regional requirements, fewer batches may be justified. Additional long-term data to support a proposed re-test period or shelf life from the primary batches may be needed during the regulatory review.

Table 1: Recommended stability data for the standard approach at submission to support the initial re-test period or shelf life for synthetics

Product Type	Batch Type	Number of Batches	Long-term Storage Condition	Accelerated Storage Condition [1]
New synthetic chemical entity drug substances and/or drug products for which a new drug regulatory submission is required	Primary	3	12 months	6 months
Existing synthetic chemical entity drug substances and/or drug products for which an abbreviated/ abridged regulatory submission is required	Primary	3 [2]	6 months	6 months

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

[2] Reduced number of batches may be justified in accordance with regional requirements.

3.2.2 Stability Data to Support the Initial Re-test Period and Shelf Life for Biologicals

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 the dependence of molecular conformation and biological activity on non-covalent as well as covalent forces that result in high sensitivity to environmental factors (e.g., temperature changes, oxidation, light, ionic content, and shear). Therefore, a stability evaluation for biologicals may necessitate complex methodologies including physicochemical, biochemical, and immunochemical procedures, and consideration of many external conditions which can affect the product potency, purity, and quality.

The recommended stability data for the standard approach at submission for biologicals are described in Table 2, Section 3.2.2. For biological drug substances and drug products, data from 3 primary batches that cover the duration of the proposed shelf life (or re-test period, when applicable) are generally expected at the time of submission. However, additional data may also be submitted during the regulatory review, in accordance with regional requirements.

When the primary batches are not production batches, a comparability assessment to production batches (per ICH Q5E) should be included in the regulatory submission. In addition, 6 months of long-term stability data on 3 production batches should be provided to confirm the representativeness of the primary stability data to establish the shelf life. These data may be provided during the regulatory review, in accordance with regional requirements.

For biologicals, data from the accelerated storage condition are utilised for product understanding and may also be used to support analytical comparability (refer to ICH Q5E). Even though these data may not be directly used to establish a re-test period or shelf

life for biologicals, it is strongly recommended to include 6 months of accelerated data in the regulatory submission to support the product's stability profile.

Table 2: Recommended stability data for the standard approach at submission to support the initial re-test period or shelf life for biologicals

Product Type	Batch Type [1]	Number of Batches	Long-term Storage Condition	Accelerated Storage Condition [2]
Biological drug substances	Primary	3	Through Proposed Shelf Life/ Re-test Period [3, 4]	6 months
Biological drug products	Primary	3	Through Proposed Shelf life [4]	6 months

1 When primary batches are not production batches, 6 months of long-term stability data on 3 production batches should be provided.

2 The minimum time period should be justified by the applicant in accordance with the selected storage conditions. A minimum of 3 time points, including the initial and final, is recommended.

3 Re-test may apply for frozen, well-characterised drug substances in accordance with *Section 13.1.1 – Re-test Period*.

4 Data through the proposed shelf life or re-test period are generally expected at the time of submission. Additional data may also be submitted during the review, in accordance with regional requirements.

3.3 Critical Quality Attributes (CQAs)

The selection of quality attributes monitored during stability studies is determined by identifying stability-indicating CQAs, other CQAs, and where applicable, pharmacopoeial CQAs (refer to *Section 3.4.3 – Pharmacopoeial Critical Quality Attributes (CQAs) and Analytical Procedures*). This approach facilitates the monitoring and control of product quality, safety, and/or efficacy throughout the re-test period and/or shelf life.

3.3.1 Stability-Indicating Critical Quality Attributes (CQAs)

The CQAs should be identified using the principles outlined in ICH Q6A, ICH Q6B, and ICH Q8–Q11. When designing a stability protocol in support of formal stability studies for 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 known to change or which have the potential to change upon storage and may impact the determination of the re-test period or shelf life and the quality, safety, and/or efficacy of the drug substance or drug product.

3.3.2 Other Critical Quality Attributes (CQAs)

Other CQAs may need to be incorporated into the stability protocol in support of the control strategy. The inclusion of these attributes should be evaluated on a case-by-case basis, considering prior knowledge and science- and risk-based assessments.

3.3.3 Recommendations for Establishing a Re-test Period and/or Shelf Life

To establish a re-test period and/or shelf life, the stability protocol should include stability-indicating CQAs and generate 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 physical forces (e.g., agitation, shear force), CQAs that may be impacted should be assessed.

Where data from development studies or prior knowledge indicate that excipient levels or their properties change on stability, potentially impacting the drug product and when applicable, drug substance CQAs (e.g., biologicals), excipients should be evaluated as part of product stability testing. In particular, excipients used as additives (e.g., surfactants, stabilisers, and preservatives) may have a functional role in maintaining the quality of the product. If there is an indication that their reaction, degradation, or depletion will adversely affect the quality of the product, these additives should be monitored during the stability programme.

Co-packaged solvents/diluents should follow the recommendations for drug products.

In accordance with the principles outlined in the ICH Q3 series, stability-indicating CQA considerations should include (a) potential interaction with the respective container closure system, (b) contact with administration or delivery devices (e.g., syringe walls, catheters, and injection needles), and (c) dispersion media (such as solvents for reconstitution or dilution).

3.3.4 Recommendations for Product Lifecycle Stability Protocols

After additional knowledge has been gained following establishment of the initial re-test period or shelf life, the stability protocol may be re-evaluated. Certain quality attributes may be removed if it is demonstrated that they do not change over time or if they are monitored via other CQAs and the change does not have a meaningful impact on quality, safety, and/or efficacy through the re-test period and/or shelf life.

Stability protocols to support the product lifecycle may be updated according to the risk-based principles outlined in *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management* and *Annex 1 – Reduced Stability Protocol Design*.

3.4 Specifications

3.4.1 Tests and Analytical Procedures

Before a formal stability study 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, where appropriate, with the elements described in 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 and/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 adequacy of the mass balance should be assessed during analytical procedure validation using degraded samples. Factors that can cause an apparent lack of mass balance should be considered, including, for example, the mechanisms of degradation, the stability-indicating capability and inherent variability of the analytical procedures.

When justified, the analytical procedures used for stability testing may differ from the release analytical procedure for the same quality attribute; for example, the use of container closure integrity testing (CCIT) during stability testing as an alternative to sterility testing.

In situations where stability-indicating CQAs are not directly tested as part of release testing (e.g., CQAs that are measured and controlled during processing as described in ICH Q8, real time release testing), analytical procedures for these attributes should be established and provided to support stability studies.

3.4.2 Acceptance Criteria

In accordance with the principles outlined in ICH Q6A and ICH Q6B, the acceptance criteria should consider all available stability information from development and manufacture of the drug substance through final drug product shelf life. 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 the shelf life.

In general, any differences between the release and shelf life acceptance criteria should be justified with data. In cases where 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 (CQAs) and Analytical Procedures

When drug substance and/or drug product pharmacopoeial monographs or general procedures are available, the associated CQAs and analytical procedures should be considered in designing a product-specific stability protocol. The product should be compliant with the applicable pharmacopoeial requirements throughout its shelf life unless appropriately justified. Flexibility allowing the use of alternative analytical procedures instead of those prescribed in pharmacopoeial official texts may be acceptable; the conditions under which this is permitted are provided by the respective pharmacopoeial or other relevant regulatory mechanisms. Any differences in the proposed analytical procedures from those in the pharmacopoeia, including stability-indicating procedures, should be scientifically justified and in accordance with the general recommendations in ICH Q4B or regional requirements.

3.5 Additional Considerations for Conjugated Products and 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.

In cases where the potency of the product is dependent on the inclusion of an adjuvant, and the vaccine is stored as an adjuvant-antigen mixture, the CQAs of the mixture (including tests of both antigen and adjuvant) should be assessed as part of the stability studies. When the adjuvant is stored separately from the antigen, stability of the adjuvant and of the antigen should be evaluated independently. When adjuvant stability data are available from the adjuvant manufacturer and it is stored per the manufacturer's tested stability study conditions, the manufacturer's stability studies may support adjuvant stability. In assessing whether the adjuvant manufacturer's stability data can support the stability of the co-packaged adjuvant, the effect of any additional processing (e.g., aliquoting) should be taken into consideration.

Stability studies for conjugated products and vaccines should 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 Drug-Device Combination Products

Stability studies for a drug-device combination product consider (a) drug product CQAs and (b) drug-device combination performance characteristics, from storage to the completion of administration (refer to *Section 11 – In-Use Stability*). The performance characteristics of the device constituent alone are outside 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 risk assessment, and compatibility with contact materials. Reduced stability protocol design principles can be applied, if appropriate (*Annex 1 – Reduced Stability Protocol Design*).

Each type of drug-device combination has its own set of quality attributes and administration-dependent performance characteristics. These attributes and characteristics should be risk assessed according to the specific design and intended use of that product to identify the critical quality attributes or characteristics that have the potential to impact the shelf life of the drug-device combination product. This risk assessment should reflect the impact of the device on the overall quality of the drug-device combination and may include data from device risk assessments, device design development studies, and prior knowledge from similar combinations of a drug product with a medical device.

Stability-indicating CQAs of the drug constituent may impact the medical device functional performance characteristics. Likewise, interactions between the drug constituent and the medical device may impact drug product stability. Formal stability studies performed and conclusions made should reflect these potential interactions. Considerations should be made regarding administration-dependent performance characteristics of the fully assembled integral or co-packaged combination of a drug product with a medical device that may be impacted by long-term storage (i.e., CQAs and characteristics that can only be assessed after assembly). Testing drug product CQAs before assembly could be accepted if justified and supported by relevant data. The storage orientation can be established based on a risk assessment.

For integral drug-device combinations, stability studies should consider drug product stability-indicating CQAs, potential interactions between the drug constituent and the device, and the fully assembled combination. For example, for a sealed cartridge in a pre-filled pen or an auto-injector, stability studies may consider the drug product stability within the cartridge as well as the drug-device combination product performance after assembly of the final product as proposed for marketing. The formal stability studies should be performed with the combination of a drug product with a medical device as proposed for marketing. Differences should be assessed and justified with respect to the impact on stability. The shelf life should be based on the shorter of the constituent parts or the final combination of a drug product with a medical device.

For a co-packed drug-device combination, the performance characteristics of the product after assembly should be considered in the formal stability protocol. It is feasible to evaluate the stability of the drug and device constituents separately unless the co-packaging configuration itself impacts the stability of the co-packaged product. For example, for a dry powder inhaler containing a drug product capsule and an inhaler device; or for an on-body injector consisting of a cartridge with the drug product and an administration device, the co-packaged product after assembly should also be considered in the formal stability protocol. 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 parts or the drug constituent part shelf life.

3.7 Risk Management

A science- and risk-based approach should be used to inform the different aspects of protocol design. This approach should align with the ICH Q9 principles.

Risk management should consider the end-to-end or cumulative impact on product quality throughout manufacturing, storage, and use, including drug substance storage, drug product storage, intermediates, short-term storage and in-use conditions. The risk assessment should consider worst-case scenarios (e.g., degradation) for both the drug substance and drug product to ensure product quality through the shelf life and use. Based on this assessment, cumulative stability may need to be evaluated, and if necessary, used to design stability studies in accordance with the other recommendations in this guideline. Refer to *Section 9 – Stability Considerations for Processing and Holding Times for Intermediates* and *Section 13.1.2 – Start of Shelf Life for Synthetic Chemical Entity Drug Products*.

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 alternative 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, stability data should generally be provided on at least 3 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 batches are provided in Table 1 in Section 3.2.1, Table 2 in Section 3.2.2, and Table 3 in Section 4.1. For additional recommendations on the container closure system, refer to *Section 5 – Container Closure System*.

4.1 Considerations for Selection of Primary Batches

Where possible, batches of drug product included in stability testing should be derived from different batches of drug substance to account for variability between 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 batches of the drug substance and drug product should be representative of the production batches and in line with the considerations outlined in Table 3, Section 4.1. Additional development batches that are representative of the primary and production batches may also be included as supporting stability data (refer to *Section 4.5 – Selection of Batches for Non-Primary Stability Studies*).

Table 3: Considerations for primary batches of drug substance and drug product when compared to production batches

	Synthetic Chemical Entities	Biologicals
Drug Substance	• Same chemical synthesis route, • Similar manufacturing process (differences justified), • At minimum, all batches manufactured at pilot scale, [1] • Meet the proposed registration specification, • Containers constructed of the same material and type of container closure system as production batches.[2]	• Same biological source (e.g., cell production system), • 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, [2] • Analytically comparable to production batches per ICH Q5E.
Drug Product	• Same formulation [3] and dosage form, • Minimum of 2 batches manufactured to at least pilot scale; [1] the other batch(es) can be smaller if justified, • Similar and representative manufacturing process that simulates the intended manufacturing process for production batches and should result in a product of the same quality as that intended for marketing, • Meet the proposed registration release specification, • Same fill unless a reduced protocol design is applied, [3] • Same container closure system as proposed for marketing. [2, 4]	• Same formulation [3] and dosage form, • Similar and representative manufacturing process that simulates the intended manufacturing process for production batches and should result in a drug product that is analytically comparable to production batches per ICH Q5E, • Meet the proposed registration release specification, • Same fill volume unless a reduced protocol design is applied, [3] • Same container closure system as proposed for marketing. [2, 4]

1 In accordance with ICH Q13, the definition of a pilot scale batch for synthetics does not apply to CM.

2 Refer to *Section 5 – Container Closure System* for additional recommendations on the container closure system.

3 Refer to *Annex 1 – Reduced Stability Protocol Design* for details around when exceptions may apply.

4 For drug-device combination products (both integral and co-packaged), drug product prior to assembly can be used if it is representative of the marketing configuration for the attributes being evaluated. Considerations should be made for the administration-dependent performance characteristics of the medical device when combined with the drug product, which may be impacted by long-term storage (refer to *Section 3.6 – Additional Considerations for Drug-Device Combination Products*).

When the long-term stability data do not cover the proposed re-test period or shelf life at the time of regulatory submission, refer to *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management* for relevant commitments.

4.2 Considerations for Vaccines

In general, production batches are expected to be used to set the shelf life of vaccines. If non-production batches are used as primary batches, the justification should be based on product knowledge, comparability studies, and risk. The recommendations for primary batches for biologicals in Table 3, Section 4.1 are also applicable to vaccines.

4.3 Considerations for Multiple Production Sites in the Initial Regulatory Submission

The stability data from each production 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, as supported by relevant data, the re-test period and/or shelf life need not be re-established at an additional production site at the time of the initial regulatory submission.

An additional production site refers to any manufacturing location proposed in the initial regulatory submission other than the drug substance and drug product site where the primary stability batches or original production batches were manufactured.

4.3.1 Considerations for Synthetics

For synthetic chemical entities, a comparison of batch data of the primary batches with relevant data from each additional production site should be provided in the regulatory submission. The amount of stability data provided for each additional 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 3 with a supporting scientific justification and risk assessment.

4.3.2 Considerations for Biologicals

For biologicals, the standard minimum stability data presented for each production site should be as outlined in Table 2, Section 3.2.2. However, for biologicals with an enhanced level of product and process understanding, an alternative approach using science- and risk-based principles 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 stress condition stability results for 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 experience as prior knowledge 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 dataset 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 3 production batches per site in accordance with *Section 15.1 – Commitment Stability Studies*.

4.4 Considerations for Continuous Manufacturing (CM) Processes

For general guidance on selection of batches for both synthetics and biologicals from a CM process, refer to ICH Q13. The drug product primary batches manufactured by CM processes should incorporate the variability described for different drug substance batches.

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 cell culture duration to capture variability.

4.5 Selection of Batches for Non-primary Stability Studies

Studies that are not a primary stability study (e.g., supportive stability studies and studies to support post-approval changes) may use primary batches or batches that are representative, as described below.

Synthetic chemical entities: Chemically synthesised drug substances should be manufactured by the same synthetic route as the proposed production batches. Drug products should be of the same formulation and manufacturing process as the proposed production batches. Differences in manufacturing process parameters should be scientifically justified.

Biologicals: Drug substance and drug product batches should be manufactured using a similar process to the proposed production manufacturing process and have acceptable analytical comparability to the production batches as appropriate for the study purpose. The analytical comparability for the non-production batches (including clinical batches) to the production batches should be consistent with the recommendations in ICH Q5E.

5 CONTAINER CLOSURE SYSTEM

For the purpose of stability studies, a container closure system comprises the primary (in contact with the product) and the secondary packaging, if the latter is intended to assure the stability of the product or has a functional administration purpose. The stability study design

should consider and include the secondary packaging when it impacts the chemical, physical, or functional attributes, unless otherwise justified (e.g., storage in secondary packaging meant for light protection only may not be necessary if samples are stored in stability chambers that offer light protection).

The formal 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 representative 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 same container closure system as proposed for marketing is strongly recommended for formal stability studies. This will ensure that the drug product 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 the product's intended shelf life. When applicable, the impact of container closure system components from which matter may migrate (e.g., ink or adhesive from labels) or leach into the product should also be considered during stability study design.

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 CQAs 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 single worst-case orientation is justified with supporting data. When drug product-container closure interactions cannot be excluded, stability studies should include samples maintained in both the inverted (or horizontal) position and 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

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 less than 12 months, 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 a drug substance or drug product with a proposed re-test period/shelf life of at least 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 the end of the proposed re-test period/shelf life.

For sterile products, the testing intervals described above are not applicable to sterility testing, which is generally performed at the initial time point, final time point, and at appropriate intervals in between (e.g., annually) to demonstrate that the product's sterility is maintained through the proposed re-test period/shelf life. Except for sterility testing at release, CCIT may be included in lieu of sterility testing in the stability protocol. Sterility testing or CCIT should be performed annually until the end of shelf life.

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

For studies under accelerated conditions, a minimum of 3 time points, including the initial and final time points, is recommended (e.g., 0, 3, and 6 months are 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 for synthetics (refer to *Section 13 – Data Evaluation* and *Annex 2 – Stability Modelling*) or are likely to be out-of-specification, additional testing is recommended. Additional testing could be conducted either by (a) including an additional less severe temperature condition (i.e., intermediate) that may be more predictive of the long-term stability and/or (b) including additional time points 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 *Annex 2 – Stability Modelling*).

7 STORAGE CONDITIONS

7.1 General Considerations

Stability of drug substances and drug products should be evaluated under storage conditions 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/or any short-term storage conditions (refer to *Section 10 – Short-Term Storage*). Advice on storage conditions to support an in-use period is detailed in *Section 11 – In-Use Stability*.

Testing at accelerated conditions and, where applicable, stress studies may be used to inform product stability by identifying degradation pathways and the intrinsic stability of the molecule, confirming the stability-indicating nature of the analytical procedures (refer to *Section 2 – Development Stability Studies under Stress and Forced Degradation Conditions* and *Section 3.3 – Critical Quality Attributes [CQAs]*) and evaluating the impact of unintended excursions in storage conditions.

Data generated under accelerated conditions may also enable stability modelling (refer to *Annex 2 – Stability Modelling*) and extrapolation (refer to *Section 13.3 – Extrapolation and Stability Modelling*). 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 or stress studies could also support that a manufacturing change did not impact the stability profile (refer to *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management*).

The impact of different humidity conditions on a product should be evaluated. In general, controlled humidity conditions are not needed when an impermeable container closure system is used (refer to *Section 7.2.1 – Storage Conditions for Products Packaged in Impermeable Containers*). Appropriate stability data under the recommended humidity conditions described in this section should be provided for any other container closure system.

The storage conditions to be applied to the different stability studies are detailed in the sections below. The equipment utilised should be qualified and capable of controlling the storage conditions 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. Excursions due to equipment failure or those exceeding defined tolerances (e.g., more than 24 hours) should be assessed, documented, and handled within the corresponding pharmaceutical quality system (PQS), and reported if judged to affect stability results.

Alternative storage conditions to those described below can be used if justified. The 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 Conditions

Room temperature refers to the general customary environment and is dependent on the climatic zone. The recommended storage conditions that are applicable to each climatic zone are outlined in Table 4.

Table 4: Storage condition recommendations for each climatic zone

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

RH = relative humidity

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

[2] For climatic zones, refer to *Section 1.3 Introduction to Guideline and General Principles*.

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

In general, it is acceptable for stability information to be generated under a more severe climatic zone storage condition defined in Table 4 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 approaches may be considered:

- Alternative long-term storage conditions for the intended climatic zone.
- A reduction in the re-test period or shelf life to ensure that the product remains within acceptance criteria.
- Evaluation of stability in an alternative container closure system.
  Evaluation of formulation and manufacturing process options.

For synthetics, 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 (40°C ± 2°C/75% RH ± 5% RH), testing at the intermediate storage condition should be conducted (refer to *Section 6 – Testing Frequency*).

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.

7.2.1 Storage Conditions for Products Packaged in Impermeable Containers

Since drug substances and drug products packaged in impermeable containers (e.g., aluminium/aluminium foil blisters, sealed glass ampoules) generally provide a permanent barrier to the 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 generally a concern for drug substances 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 shown in Table 5. 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.

Table 5: Storage condition recommendations for aqueous-based products packaged in 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/NMT 25% RH
30°C ± 2°C/35% RH ± 5% RH	Not applicable	

NMT = not more than; RH = relative humidity

If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition. If 25°C ± 2°C/40% RH ± 5% RH is the long-term condition, it is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH. A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after 3 months storage at 40°C ± 2°C /not more than (NMT) 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after 3 months storage at 40°C ± 2°C/ NMT 25% RH may be acceptable, if justified.

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

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

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

Example: An Approach for Determining Water Loss.

For a product in a given container closure system, container size and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio determined by calculation as shown in Table 6. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated. If a linear water loss rate is not observed or if no water loss is observed at the alternative relative humidity, the water loss should be determined at the reference relative humidity.

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 6: 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

RH = relative humidity

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

The ratios described in Table 6 are for illustrative purposes. In situations where different alternative relative humidity conditions are applicable, the ratio of water loss rates at a given temperature may be calculated using the formula in footnote 1 of Table 6.

7.3 Considerations for Products Intended to be Stored at Refrigerated Temperature Conditions

Recommendations for drug substances and drug products intended for long-term storage under refrigerated conditions are provided below (Table 7). Accelerated conditions are intended to demonstrate the effect of temperature, and active humidity control may not be needed when justified.

Table 7: Storage under refrigerated conditions

Long-term	Accelerated
5°C ± 3°C	25°C ± 2°C/60% RH ± 5% RH

RH = relative humidity

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

When a significant change or an out-of-specification result occurs within the first 3 months of testing under accelerated conditions, a discussion should be provided to address the effect of shipment and handling and, where appropriate, this information should also be included in the labelling (refer to *Section 14 – Storage Statements in Labelling*). For synthetics, when accelerated stability studies are intended to support shelf life extrapolation per the decision tree (*Annex 2, Section A2-2.4 – Extrapolation for Synthetic Chemical Entities Based on the Decision Tree*), it is considered unnecessary to continue testing a product under accelerated conditions through 6 months when a significant change has occurred within the first 3 months.

7.4 Considerations for Products Intended to be Stored at Frozen Temperature Conditions

For drug substances and drug products intended for long-term storage under frozen conditions, the long-term storage conditions should reflect the labelled storage conditions as determined for the product. When the labelled storage conditions include considerations for shipment and/or short-term storage, stability data should be provided to support the conditions covered by the label. For example, a drug substance intended for frozen long-term storage condition at -20°C or below should have stability data to support the proposed duration and a justification for an appropriate temperature range of storage at the intended condition.

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 period should be conducted to address the effect of excursions outside the proposed labelled 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 the 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 an unacceptable change in quality 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 potentially 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 is typically included as part of the forced degradation evaluation that 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 Degradation Conditions*).

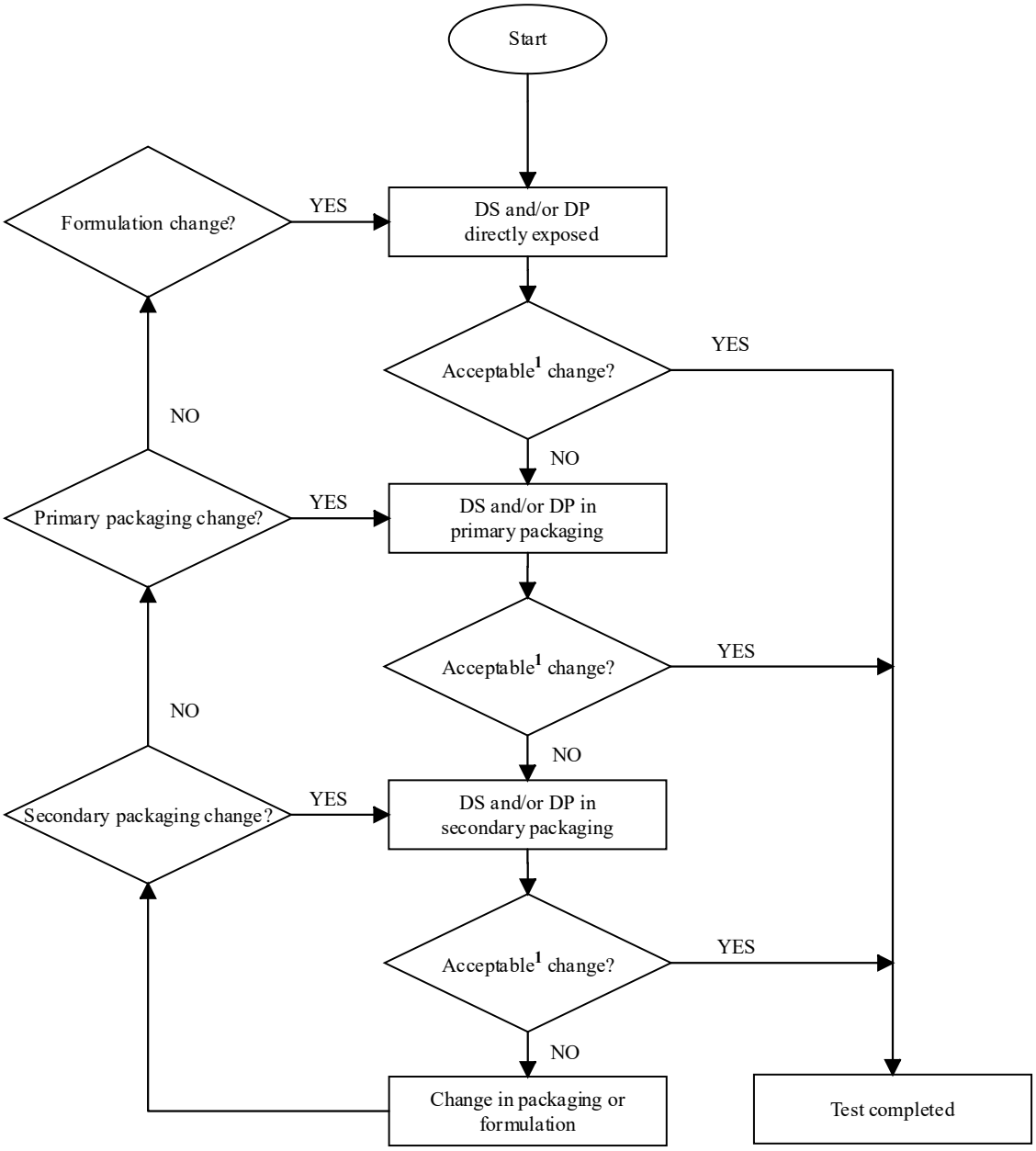
- Confirmatory photostability studies: Studies performed when a risk of photodegradation has been identified. The purpose of the studies is to establish the photostability characteristics, to understand the ability of the primary or secondary packaging material to protect light-sensitive products, and to understand 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:

1. Tests on the drug substance and/or drug product directly exposed, when applicable.
2. If necessary, tests on the drug substance and/or drug product in the primary packaging.
3. If necessary, 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 proposed for marketing and then in the secondary packaging, if applicable. If the product is known to be photosensitive (e.g., most biologicals), these studies can be conducted simultaneously, using a science- and risk-based approach. The extent of testing should be established by assessing whether acceptable change (including 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).

Figure 3: Decision flow chart for systematic photostability testing



DS = drug substance; DP = drug product

[1] Including no change.

8.2 Forced Photodegradation

As forced photodegradation is an integral part of the forced degradation strategy, details on the concepts, study design considerations, and interpretation of results can be found in *Section 2 – Development Stability Studies Under Stress and Forced Degradation Conditions*. For details on radiation sources and light exposure conditions for forced photodegradation 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 recommendations 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 the 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, Section 8.1).

For synthetic chemical entities, confirmatory photostability testing is generally performed on one representative batch of the drug substance and one of the drug product, while for biologicals, testing is generally performed on one representative batch of the drug product. Confirmatory testing for both chemical entities and biologicals is typically conducted in the primary packaging and, if necessary, the 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 and/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 typically only be conducted on the directly exposed drug product.

If the results from the confirmatory study batch are not conclusive in terms of photostability, 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 NMT 3 mm. 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). Lyophilised products may be tested in the intended storage vial. In general, the samples should be positioned to provide maximum area of exposure to the light source.

If testing of the product in the primary and 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 the intended purpose) for any changes in physical, chemical, or biological properties, including drug substance content (assay) or potency and degradant products 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 any protected samples used as dark controls (e.g., wrapped in aluminium foil) 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 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, such as formulation change, redesign of primary and/or secondary packaging, a reduced re-test period or shelf life

of the drug substance or drug product (in conjunction with long-term stability data) or a change in labelling for storage and use (refer to Figure 3, Section 8.1).

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 and control the spectral characteristics of the light, cumulative light exposure, temperature, and humidity 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 Standard daylight illuminant D65 (D65)/Indoor daylight standard ID65 (ID65) emission standard (as currently defined in the International Organization for Standardization (ISO)/International Commission on Illumination (CIE) 18909:2022) (23), an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp, including appropriate filter(s) is recommended as a radiation light source.

Option 2:

A combined exposure to both cool white fluorescent and near UV lamps is capable of producing a light exposure similar to the D65/ID65 emission standard. A significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm.

Option 3:

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

In confirmatory studies, to assess the effects of light under controlled conditions during manufacturing, storage, and in-use, samples should be exposed to light providing a total light exposure of not less than 1.2 million lux hours and an integrated near UV 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 can be determined by measuring the light exposure and defining the average light exposure and UV energy (e.g., in lux hours 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 be 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 GDP.

The processing time can be considered the established time period needed to perform a manufacturing step or series of steps and should take into consideration compatibility with manufacturing equipment. Holding time can be considered the established time period for which materials (i.e., 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 confirm that they can be held, pending the next processing step, without having results outside the established control strategy. A protocol,

procedure, or programme 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 conditions and time that the intermediate may be held before further processing. 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, taking into account the following considerations:

- Holding time studies should include an assessment of physicochemical stability and, when applicable, the microbial control strategy.
- If the temperature and humidity conditions used during these studies do not correspond with the storage conditions described in *Section 7 – Storage Conditions*, alternative conditions should be justified.
- If the product or intermediate is sensitive to light exposure that may occur during storage, it should be confirmed that the controls in place are sufficient to limit exposure to acceptable levels.
- If more than one production site is involved, the stability studies should also consider the transportation conditions of the intermediates.
- Where there are multiple holding times and a potential risk to the stability of the product is identified, the cumulative impact may need to be evaluated, and if necessary, used to design stability studies and process validation.

When a drug substance or drug product intermediate is packaged and stored outside of the manufacturing process activities (e.g., antibody prior to conjugation) or 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.

For drug product produced by batch processes (i.e., not by CM processes), it is expected that the data to support the holding times are generated and are representative of the overall process. If the data to support the holding times were not generated on a production batch, these data should be verified on production batches and managed within the PQS. If CM processes are

used, the principles outlined in ICH Q13 should be followed, and any holding times should be evaluated on batches representative of the production process.

Stability recommendations for intermediates, including considerations that are specific to 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 be managed within the PQS. 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, the principles described below also apply, as appropriate.

When considering drug product intermediates, 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 established, the processing times and maximum holding times for drug product intermediates should be included in the description of the manufacturing process. When applicable, the information to support the processing and holding times should be included in the regulatory submission.

Holding time studies should be performed based on the duration of the hold and on a risk assessment. Evidence of the suitability of the holding times, together with the proposed container that is representative of the container used in production, the storage period, and transportation conditions should be included in the regulatory submission, as required. Where intermediates are transported between production sites and a risk is identified, the transportation conditions should be included in the description of the manufacturing process, as required.

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, define process limits, and establish holding times that assure their stability within the conditions of the developed manufacturing process.

A holding time study for a biological will typically consider two elements: (a) physicochemical stability and (b) the 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 stability-indicating CQAs, such as purity and impurity, and other CQAs. Microbial control should be demonstrated for the manufacturing process of production 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.

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.

10 SHORT-TERM STORAGE

Short-term storage is a defined duration and condition under which a drug product can be held outside of the long-term storage condition. It is intended for the convenience of the patient or healthcare professional, in accordance with regional requirements. Unlike the in-use period, short-term storage does not involve breaching the primary container closure or any necessary manipulation required for administration. For example, short-term storage could enable a patient to store a refrigerated drug product at room temperature conditions for a specified duration of time. Short-term storage is optional; however, when claimed, the duration and condition should be included in the drug product labelling (refer to *Section 14 – Storage Statements in Labelling*).

The design of specific short-term storage stability studies should follow the general principles applied to formal stability studies (refer to *Section 3 – Protocol Design for Formal Stability Studies*) and should consider all relevant climatic zones. The number of batches and the considerations for aged samples should be based on the general principles described for in-use stability studies (refer to *Section 11.2.1 – Selection of Batches for In-Use Studies*). The applicant should demonstrate that a drug product with proposed short-term storage will remain within the shelf life specifications. The short-term storage duration is not intended to be applied beyond the shelf life of the drug product. If the drug product can be returned to long-term storage conditions after an acceptable period of short-term storage, supporting data should be provided as part of the formal stability studies.

The applicant may justify alternative strategies, such as modelling (refer to *Annex 2 – Stability Modelling*), to support short-term storage. Once a short-term storage condition is established, it does not need to be re-evaluated unless there is a post-approval change that is likely to impact stability (refer to *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management*).

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 in accordance with 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 drug-device combinations containing drug product intended for multiple administrations or doses. Products packaged in single-use containers 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 conditions (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.

For products requiring preparation and for multi-dose products, the conditions of use may pose a risk to drug product quality in terms of their 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, unless a scientific- and risk-based justification demonstrates that such testing is not necessary to support product quality. 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, which are applicable across multiple product types. The material in contact with the product and used in the preparation and administration should be demonstrated to be suitable for use with the drug product.

Under some circumstances, these studies may need to be repeated when 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 the change should be performed according to *Section 15.3 – Product Lifecycle Stability Studies*.

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 – Protocol Design for Formal Stability Studies*. 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, the 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 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 (e.g., for solid oral dosage forms, the applicant may justify the use of open dish studies instead of an in-use study).

Alternative approaches to protocol design may be considered when appropriately justified.

11.2.1 Selection of Batches for In-Use Studies

Generally, in-use stability data should be provided on 2 representative batches of 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 chosen should be towards the end of its shelf life. If such results are not available, 1 batch should be tested at the final point of the submitted stability studies. If

aged batch data are not available at the time of filing, a commitment to provide the data or a justification for why those data may not be needed 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 proposed in the labelling. For drug products with different fill volumes, strengths, or presentations, a representative worst-case 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 – Critical Quality Attributes [CQAs]*). 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. The acceptance criteria should be established taking into consideration the specifications; however, differences may be justified.

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

For biologicals, the physical and chemical CQAs selected should be appropriate to the individual dosage forms (24). For example, physical and chemical CQAs of protein content, appearance, clarity, colour, visible particles, sub-visible particles, and product-related variants or impurities should be considered for testing, as applicable. Potency testing, or where applicable an analytical procedure covering the mode of action, should be included, and potential analytical limitations should be understood. Microbial control should be addressed for the duration of the proposed in-use period for biologicals.

For any drug product for which microbial control is appropriate, common recommended testing includes a Preservative Efficacy Test (PET)/Antimicrobial Effectiveness Test (AET), a microbial challenge study, or a microbial enumeration procedure (e.g., bioburden). In lower risk situations, it may be possible to justify the absence of microbial testing 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 is 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 (i.e., those used for the first time in a drug product or through a new route of administration), and vaccine adjuvants. Novel excipients and adjuvants are discussed due to their significant potential impact on the stability and quality of the drug product.

12.1 Reference Materials

Reference materials (as defined in ICH Q2 and ICH Q14) that are used to control the quality attributes of a stored intermediate, drug substance, or drug product should be sufficiently homogeneous 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 are different from the stored intermediate, drug substance, or drug product, a specific reference material stability programme may be needed, with an established use period that reflects the differences. Externally sourced, well-characterised reference materials (e.g., pharmacopoeial, national/international reference materials) should follow manufacturer recommendations for storage, and, where applicable, the stability of these reference materials

should be periodically verified through an appropriately established requalification protocol managed within the PQS.

Stability data should be available to support the use period of the in-house reference material. Stability data for in-house reference materials are managed within the PQS. In addition, for biologicals these data are generally provided with the regulatory submission. Extrapolation may be applicable to reference materials with a well-understood stability profile and with little or no change over the duration of storage. Justification for extrapolation should be based on a science- and risk-based approach.

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/or requalification according to an 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 those used to store the drug substance or drug product, these 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 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 CQA (e.g., potency) is being controlled relative to a reference material, a risk-based approach, including consideration of more stringent stability acceptance criteria and trend analyses, may be needed 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 – Protocol Design for Formal Stability Studies*, *Section 6 – Testing Frequency*, and *Section 7 – Storage Conditions*). If the novel excipient itself is a protein, additional risk assessments and data from development studies should be provided to clarify the known degradation profile of the excipient and its impact on the drug substance or drug product (e.g., excipient-product interaction, quantity of intact excipient in the drug product, and impact on drug product immunogenicity). This information should be used to inform the design of the formal stability protocol.

12.3 Vaccine Adjuvants

Adjuvant stability data should be provided in the regulatory submission 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.

Adjuvanted vaccine stability studies will depend on the formulation/presentation, where vaccine drug product formulated with the adjuvant will have different considerations to formulations where the adjuvant is provided in a separate vial from 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 the shelf life of the adjuvanted vaccine in the primary container are required. In the case of adjuvanted vaccines that depend on antigen adsorption to the adjuvant (e.g., aluminium hydroxide/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 the storage duration and storage conditions of each vaccine component.

The in-use stability of the adjuvant-antigen mixture should be assessed 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 the 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 comprehensive stability data evaluation should take into consideration any stored intermediates, process hold times, and any short-term storage outside of the long-term storage conditions, including the risk of excursions from the storage conditions, and manipulations of the product to the completion of administration to the patient (in-use stability). A systematic approach should be adopted in the presentation and evaluation of the stability information.

This section addresses the evaluation of stability data to establish a re-test period or shelf life for the drug substance and the shelf life for the drug product based on long-term data at the recommended storage condition. Refer to *Section 3 – Protocol Design for Formal Stability Studies* for the minimum stability data at the time of submission. Alternatively, when there are limited long-term stability data at the recommended storage condition, the initial re-test period or shelf life beyond the available real-time stability data can be proposed based on:

- 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 (refer to *Annex 2, Section A2-2.4 – Extrapolation for Synthetic Chemical Entities Based on the Decision Tree*). Note that for biologicals, the decision tree approach is not considered suitable due to the inherent differences in degradation mechanisms and other structure/function differences within biologicals.
- Limited extrapolation for certain well-characterised biological drug substances may also be considered (refer to *Section 13.3.2 – Extrapolation for Biologicals*).
- Use of enhanced stability modelling methodologies to predict or extrapolate the stability profile past the point of the available real-time data, for synthetic chemical entities and biologicals (refer to *Annex 2, Section A2-3 – Enhanced Stability Modelling*).

While extrapolation and enhanced stability models may be used to predict the initial re-test period or shelf life, these approaches should be considered as part of a comprehensive stability programme and are not intended to replace long-term stability studies.

When the principles for extrapolation and modelling are considered to apply to product types requiring specific scientific and risk considerations, such as ATMPs or vaccines, the applicant is encouraged to seek early engagement with the regulatory authority.

Guidance is provided for the data evaluation of drug substances and drug products that have stability data from at least 3 primary batches with batch as a single-factor and, for multi-factor products, with a full stability design (for example, products with the same drug substance at different fill volumes, varied concentration, or container closure system dimensions). Multi-factor products with reduced design studies are discussed in *Annex 1 – Reduced Stability Protocol Design*.

13.1.1 Re-test Period

The re-test period is a period of time during which the drug substance is demonstrated to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided the drug substance has been stored under the defined conditions. The re-test period is established and confirmed via a formal stability study protocol, according to the principles outlined within this guideline. The re-test period applies to all future batches of the drug substance manufactured under similar circumstances. Refer to ICH Q7, ICH Q7 Q&As, and WHO TRS 1010 – Annex 10 (19) for additional information on managing re-test periods.

After the assigned re-test period has ended, an individual batch of drug substance can be tested for compliance with the specification (refer to *Section 3.4.2 – Acceptance Criteria*) and then used immediately (e.g., 30 days) for the manufacture of a drug product. A representative sample from this batch should be taken for the purpose of performing a re-test. The batch can be re-tested multiple times and a different portion of the batch used after each re-test, so long as it continues to comply with the specification. A re-test period is typically applicable to stable synthetic drug substances as an alternative to establishing a shelf life. For synthetic drug substances known to be labile, a shelf life may be more appropriate.

When justified, a similar approach may also be proposed in certain cases for the drug substances of well-characterised biologicals with a well-understood stability profile that are stored frozen and show little to no change in product quality over the duration of storage. The

justification for a re-test approach is supported by information such as long-term stability data of representative batches, prior knowledge, trend analyses of CQAs, freezing and thawing studies, and relevant characterisation data, as applicable. The impact of re-testing over an extended time-period on the drug product quality needs to be risk-assessed. A re-test period is generally not appropriate when extrapolation or modelling is proposed for biological drug substances.

The start of the re-test period or shelf life for synthetic or biological drug substances, as applicable, is generally managed under PQS. Additionally, for biological drug substances, the manufacturing step at which the re-test period or shelf life begins should be indicated in the regulatory submission (e.g., start of the re-test period or shelf-life is initiated at the time of filling), in accordance with regional requirements.

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 the drug substance with other ingredients.

In accordance with regional requirements, consider the following approach:

- 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 manufacture.

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, the approach for determining the start of shelf life for the drug product should be declared and justified, taking into account the cumulative impact of the maximum intermediate storage time on product quality (refer to *Section 9 – Stability Considerations for Processing and Holding Times for Intermediates*).

13.1.3 Start of Shelf Life for Biological Drug Products

The start of shelf life for biological drug products begins on the date of manufacture (e.g., the date of filtration and/or filling for a liquid or lyophilised drug product). When the drug product filling operation takes place over more than one day, 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. The approach for determining the start of shelf life for the drug product should be declared.

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 evaluation should include data from all primary stability studies, any available data from production scale studies, and be 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 purpose 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; results from semi-quantitative or qualitative analytical procedures, which may not be amenable to statistical analysis, should also be evaluated. Any exclusion of quantitative attributes tested in accordance with the formal stability protocol from the statistical evaluation for the re-test period or shelf life should be justified. The degree of variability across individual batches, as well as the number and frequency of data time-points, affects the certainty that a future production batch will remain within specification throughout the established re-test period or shelf life (25).

There are many valid statistical methods to evaluate stability data to set a re-test period or shelf life from batches of drug substances, intermediates, or drug products. The statistical methodology used should be justified as suitable for the product type, the dataset used for the analysis (batches, study design factors), 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 Individual Batches

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 appropriately (e.g., log) transformed data that follow a linear pattern at the recommended storage condition, an approach for evaluating the data is a linear regression analysis. The appropriateness of the assumed linear relationship over time and the normal distribution of variables can be assessed by evaluating the residuals of the regression line to determine the goodness-of-fit (refer to *Annex 2, Section A2-2.1 – Evaluation of Stability Data in Single-Factor, Full Design Studies Using Linear Regression Models*). The 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 into one overall estimate of a proposed re-test period or shelf life.

13.2.2 Combining Data from Multiple Batches

Batches may be combined to gain a better understanding of product stability across a population of batches. An appropriate statistical approach should be prospectively defined and justified to evaluate whether data from different batches can be combined, with clear identification of meaningful differences to ensure that the evaluation focuses on differences that are relevant (28, 29). 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 (30).

13.2.3 Scale Transformation of Data

When the degradation kinetics are complex and decelerating (e.g., a biphasic degradation profile characterised by a fast initial rate followed by a slower longer-term rate or when the data 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. It should be noted that in some instances, when a linear function is fitted to plateauing data, data points beyond the plateau could skew the regression line towards later time points. 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, with justification. In some cases, a non-linear regression can better reflect the true relationship. When scale 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 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 (refer to *Section 13.2.5 – Testing to Combine Batch Data per Individual Combination* and *Annex 2, Section A2-2.1 – Evaluation of Stability Data in Single-Factor, Full Design Studies using Linear Regression Models*).
- 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 (refer to *Section 13.2.6 – Testing to Combine Data for All Factors and Factor Combinations*).

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's initially proposed shelf life.

When 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.

13.2.5 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 studies (refer to *Annex 2, Section A2-2 – Statistical Evaluation of Stability Data from Single or Multi-Factor Study Designs*). For example, for a drug product available in 2 strengths and 4 container sizes, 8 sets of data from the 2 x 4 strength-size combinations can be analysed, and 8 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.

13.2.6 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. When batches, strengths, container sizes, and/or fills are combined into a single analysis of covariance (ANCOVA), the amount of data increases and the shelf life may be longer because of the increased precision in the estimates, potentially leading to narrower statistical intervals (e.g., confidence limits, tolerance intervals, prediction intervals, or other tools). 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.

13.3 Extrapolation and Stability Modelling

Extrapolation is the practice of using a known dataset to infer information about future data and is a form of stability modelling that, under certain conditions, may be applicable to synthetics and biologicals. Extrapolation may be performed using basic models, including statistical tools in common use (*Section 13.2 – Statistical Evaluation of the Long-Term Storage Condition Stability Profile to Establish the Re-test Period or Shelf Life*), or may employ enhanced models, as described in *Annex 2 – Stability Modelling*. 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 of 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

models, and the existence of relevant supporting data that may include additional time points, additional batches, or prior knowledge. Relevant supporting data may include satisfactory long-term data from development batches that are (1) made with a comparable formulation, (2) manufactured on a different scale, or (3) packaged in a container closure system similar to that of the primary stability batches. When data indicate that extrapolation is not appropriate, the re-test period or shelf life should be based on long-term data.

For synthetics, certain quantitative chemical attributes (e.g., drug substance content (assay), chemical degradation products, preservative content) for a drug substance or drug 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, water content) 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 presented in *Annex 2 – Stability Modelling* (Figure 4 in Annex 2, Section A2-2.4) would not be recommended for biological products because biological and immunological attributes are generally not amenable to extrapolation by this approach, 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 13.3.2 – Extrapolation for 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- and risk-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 A2-2 – 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.

When there is adequate product knowledge, including understanding of the degradation profile, applicants may also consider enhanced modelling techniques as described in *Annex 2, Section A2-3 – Enhanced Stability Modelling*.

When the proposed shelf life is extrapolated beyond available long-term data from primary stability studies, the primary stability studies and any other commitment stability studies should be continued post-approval to confirm the shelf life with long-term data in accordance with recommendations in *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management*.

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 (e.g., re-evaluation of the initially predicted shelf life).

After extrapolation, lifecycle considerations should follow *Annex 2 – Stability Modelling* and *Section 3.7 – Risk Management*, as applicable.

13.3.1 Extrapolation for Synthetic Chemical Entities

To support extrapolation, the available data should be evaluated using a systematic approach, including statistical analysis where the data are amenable. A decision tree is provided as a tool for appropriate data extrapolation beyond the period covered by long-term stability data (refer to *Annex 2, Section A2-2.4 – Extrapolation for Synthetic Chemical Entities Based on the Decision Tree*, Figure 4). 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. It 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. This approach may provide limited extrapolation, though greater extrapolation beyond these stated limits may be possible using enhanced modelling methodologies (refer to *Annex 2, Section A2-3 – Enhanced Stability Modelling*).

When a synthetic chemical entity drug substance or product is stored frozen, with no observable or no statistically significant change over time for the available data of all CQAs 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, when applicable, the stability modelling approaches described in *Annex 2 – Stability Modelling*.

13.3.2 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 CQAs are known, and their corresponding criticality and residual risks evaluated to ensure patient safety. When justified, 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, held at the proposed storage condition, to a maximum of 12 months beyond available long-term data. The starting point for this proposed extrapolation would generally be supported by the longest time point reached by all 3 primary stability batches.

Justification should include a science- and risk-based approach to fully support the proposed extrapolation, including data available on representative batches that have long-term data to the end of the proposed shelf life that are analytically comparable to primary stability batches.

Justification should also include statistical analysis (such as using linear regression with a 95% confidence limit) of available long-term data on representative batches (refer to *Section 4 – Selection of 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, the impact of degradation of the molecule on the drug product, knowledge of the impact on stability due to the manufacturing process and storage (e.g., rate of freezing and thawing of the drug substance), the container closure system, drug substance concentration, and formulation to support the extrapolation.

Alternative approaches for well-characterised biological drug substances (e.g., including for those stored under conditions other than frozen) can be proposed and justified for extrapolation and/or shelf life prediction as described above based on appropriate prior knowledge and/or enhanced stability modelling.

Using the enhanced stability modelling approaches as described in *Annex 2, Section A2-3 – Enhanced Stability Modelling*, greater extrapolation beyond current limits may be possible. Although enhanced modelling strategies are not currently linked to an upper limit for shelf life prediction, applicants should provide a scientific justification for the proposed shelf life as outlined in *Annex 2 – Stability Modelling*.

The general principles outlined here for extrapolation of frozen-stored drug substance 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 on patient safety and efficacy. Additionally, while shelf life for biological products is generally established based on long-term data, for biological drug products with a well-understood degradation profile, applicants are encouraged to consider enhanced modelling techniques as described in *Annex 2, Section A2-3 – Enhanced Stability Modelling*.

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.

13.4 Data Presentation

The applicant should follow ICH M4Q for data presentation expectations. In general, stability data for all tested attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be provided. 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 STORAGE STATEMENTS IN LABELLING

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

A storage statement should be established for the labelling in accordance with relevant regional requirements, based on the evaluation of stability data with respect to the climatic zone where the drug substance and/or drug product is intended to be stored, shipped, or used. When

applicable, storage statements should reflect information related to the in-use period and storage conditions (refer to *Section 11.3 – Labelling of 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*).

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 specific instructions may be provided on the product labelling, where relevant.

Transient temperature excursions outside of the label storage conditions may be found acceptable if justified and supported by stability data. Each excursion should be managed as a deviation, documented, and handled within the corresponding PQS.

An assessment of the risk and impact of handling, transport, and storage excursions outside the label claim requires a comprehensive knowledge of the supply chain and an understanding of the drug substance and drug product stability profile. Data from stability studies, including accelerated studies, stress testing (refer to *Section 2 – Development Stability Studies under Stress and Forced Degradation Conditions*), or other relevant data (e.g., transport simulation studies when appropriate) can be used to evaluate the impact 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.

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 initial development through marketing until the product's discontinuation. Lifecycle management in the context of stability includes initial stability testing, the determination of re-test period and/or shelf life, ongoing (annual) stability studies, 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, the general principles may also apply to intermediates that require studies to support re-test period/shelf life or holding times.

Commitment stability studies should include a proposed action for informing the regulatory authority for cases where data from such stability studies fall outside the acceptance criteria, as confirmed through a quality investigation, 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 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. When all batches used in the primary stability studies are production batches and stability data cover the proposed re-test period and/or shelf life, a commitment stability study is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the regulatory submission includes long-term data from stability studies of less than the re-test period or shelf life for at least 3 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 3 production batches, a commitment stability study should be conducted to generate stability data on at least 3 production batches in total. Commitment stability studies under the long-term storage conditions should be initiated or continued through the proposed re-test period and/or shelf life and, if applicable, under the accelerated storage conditions through to 6 months in accordance with the expectations in *Section 3 – Protocol Design for Formal Stability Studies*.
- For synthetics, if the regulatory submission does not include any stability data on production batches, a commitment stability study should be conducted to generate stability data on at least 3 production 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 in accordance with the expectations in *Section 3 – Protocol Design for Formal Stability Studies*.

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-indicating CQAs at the approved storage conditions over the product lifecycle. These studies also allow for the monitoring of other CQAs to examine trends in the stability data, confirm the appropriate storage conditions relevant for the product, and 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 (refer to *Section 5 – Container Closure System*) should be added to the ongoing stability programme per year, unless none is produced that year. Ongoing stability studies are generally managed within the PQS, unless a regulatory authority expects the submission of the information and data. Each production site should maintain an ongoing stability programme in accordance with GMP. 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 in accordance with the ongoing stability programme. As product knowledge is gained, the applicant may consider removal of testing of attributes not related to stability and/or reduce testing time points based on a risk assessment as detailed in *Section 3 – Protocol Design for Formal Stability Studies*. Reductions, including bracketing and/or matrixing approaches, based on stability knowledge and risk assessment should be justified in the regulatory submission, when applicable, as detailed in *Annex 1 – Reduced Stability Protocol Design*. Prior to modifying the reduced design post-approval, the manufacturer should consider whether the protocol can continue to adequately assess product stability. 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 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, where applicable.

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-indicating CQAs and other critical quality attributes of the commercial drug substance or drug product under the labelled storage, handling, and use conditions.

A risk assessment should be conducted (refer to *Section 3 – Protocol Design for Formal Stability Studies* and *Annex 1 – Reduced Stability Protocol Design*) and can be used to justify the change and determine the need for 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 established re-test/shelf life may change:

- **Scenario 1**: A risk assessment indicates that the proposed change(s) will not have an impact on the stability profile (e.g., a change to a comparable analytical procedure, a change in outside cap colour). Stability data in this case are unnecessary, and the re-test

period or shelf life will not be re-established. 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., a manufacturing process change, a change in formulation). A stability study, a stability risk assessment, or a combination thereof may be appropriate to support these changes. 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 conditions 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 conditions may need to be re-established per recommendations in *Section 3 – Protocol Design for Formal Stability Studies* to *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 to confirm that 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), not to 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.
    - If a risk assessment or an initial set of stability results do not allow for an understanding of the impact on the re-test period/shelf life, the re-test period/shelf life and storage conditions need to be re-established based on the post-change stability data.

Product lifecycle stability data provided 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). If the applicant anticipates that an extension will be made, the protocol may include additional time points beyond the initial re-test period/shelf life. Justification should be provided when a

shelf life reduction is proposed as a post-approval change. This justification should be based only 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 the drug substance, intermediate, and/or final drug product. Additional science- and risk-based considerations and approaches for identifying stability-indicating CQAs, 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.

The applicant should apply an appropriate stability strategy that demonstrates that 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-indicating CQAs 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 a comparability study for a biological product) to demonstrate the understanding from the process/product change.
- A risk assessment demonstrating that an understanding of the impact on any stability-indicating CQAs and other CQAs can support limited long-term data for post-change material while claiming the same re-test period/shelf life as the pre-change material.
- A full evaluation of stability-indicating CQAs and other CQAs 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 vapour 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 a primary/secondary packaging or in-use conditions and should follow the same considerations as discussed above and in *Section 8 – Photostability* and *Section 11 – In-Use Stability*.

If specific tests or time points from the primary stability studies had been removed for the ongoing stability protocol, these may need to be evaluated and restored for the stability studies used to support a PAC.

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

This section addresses the recommendations on what should be submitted regarding the 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 the scope of a new dosage form are new products with a 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 *Section 3.2 – Stability Data to Support the Initial Re-test Period and/or Shelf life According to the Standard Approach*). In certain justified cases, based on prior knowledge and an established stability profile, a science- and risk-based, reduced stability dataset at submission may be acceptable (e.g., 6 months of accelerated and 6 months of long-term data for a new dosage form for a synthetic chemical entity per *Section 3.2.1 – Stability Data to Support the Initial Re-test Period and Shelf Life for Synthetics*). 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.

ATMPs:

Advanced Therapy Medicinal Products.

Bracketing:

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

Container Closure System:

The sum of packaging components that together contain and protect the product. This includes primary packaging components (in contact with the product) and, if applicable, secondary packaging components (refer to *Section 5 – Container Closure System*).

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 Action and Preventive Action (ICH Q12).

CM:

Continuous manufacturing (ICH Q13).

CQA:

Critical Quality Attribute (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 3 representative batches of the drug substance or at least 3 representative 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 to establish or confirm a re-test period or a shelf life.

GDP:

Good distribution practices.

GMP:

Good manufacturing practice.

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 undesired 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 the conditions of the manufacturing process. For the purposes of this stability guideline, bulk drug products are considered intermediates.

LED:

Light-emitting diode.

Long-Term Studies:

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 consideration of the margin of analytical error.

Matrixing:

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

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 Haynes (31) can be used.

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 the examination of 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 drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For example, for synthetic 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, otherwise adequately justified. For biologicals, the steps of upstream and downstream processing should be identical except for the scale of production.

PAC:

Post-approval change.

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 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 at 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-indicating CQA and other CQA 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 the manufacture of a given drug product, provided the drug substance has been stored under the defined conditions. 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. The classification of a container as semi-permeable depends on the nature of the container material, design, and the characteristics of the product and solvent system. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (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.

Stability Model Validation:

The process of determining the suitability of a model by demonstrating the fit of the data used to develop the model and by challenging it with independent test data and comparing the results against predetermined performance criteria.

Stability Model Verification:

The process of ensuring the model is applied 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.

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 the drug substance, and develop and confirm the stability-indicating nature of the analytical procedure.

Supporting Data:

Data, other than those from formal stability studies, which support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include (1) results from supportive stability studies; (2) 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; (3) information regarding test results on containers; and (4) other scientific rationales.

Supportive Stability Studies:

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 the 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), or 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. Reduced protocol designs applied in the original regulatory submission should be followed until there is a change that has an impact on the design factors (e.g., strength/concentration). If a reduced protocol design is introduced after the original regulatory submission, change management procedures should be followed (refer to ICH Q10) in accordance with regional requirements.

This Annex specifically 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 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). 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., refer to *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management* to support post-approval changes).

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. The conditions described in this Annex are sufficient justification for use in certain cases, 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 risk-based scientific justification should precede the use of more than one reduced design principle together in one design. Any reduced design should have the ability to adequately predict the product shelf life. 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 in the design. Adjustments to the statistical analysis may be necessary, as a result of the change to the study design. 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 the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Bracketing can be applied to different container sizes and/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 formulations of a biological of different concentration, fill volume, or container size, unless there are additional considerations for excluding some complex biologicals or live vaccines, and (4) solutions, suspensions, and solid dosage forms for oral use of different strengths with formulations that differ only in minor excipients (e.g., colourant, flavouring).

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 design factors remain constant. However, when both container size and fill are varied simultaneously, it should not be assumed that testing only the largest and smallest containers will adequately represent the full range of potential variability within the container closure system. In such cases, a more comprehensive evaluation may be necessary to ensure that all relevant configurations are appropriately assessed for their impact on 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, moisture vapour transmission 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 type (e.g., material of construction, type of coating) varies. Justification could include a discussion of the relative permeation rates of the bracketed container closure systems. Special consideration of water loss 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. Stability commitments in accordance with *Section 15 – Stability Considerations for Commitments and Product Lifecycle Management* should reflect the proposed commercial presentations.

A1-3.1.3 Design Example

An example of a bracketing design is given in Table 8. This example is based on a product available in 3 strengths and 3 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 (e.g., synthetics and biologicals).

Table 8: 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

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 is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes

that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified, for example, covering different batches, different strengths, and different sizes of the same container closure system.

When secondary packaging 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, (3) oral solutions and suspensions of different strengths with formulations that differ only in minor excipients (e.g., colourant or flavouring), (4) biologicals of different concentration and fill volume, (5) biologicals of different concentration with different size containers or pre-filled syringe sizes, and (6) relative amounts of excipients (e.g., minor variation in the concentration of the filler). Justification should generally be based on supporting data. For example, to matrix across 2 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, 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 3 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 3 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 2 strengths (50 mg and 75 mg) are shown in Table 9 and Table 10. The terms one-half reduction and one-third reduction refer to the reduction strategy initially applied to the full study design for time points excluding the initial, 12-month and final time points. 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. The reductions shown below are less than one-half and one-third due to the inclusion of full testing of all factor combinations at some time points. Note that the examples could represent multiple product types (synthetics and biologicals).

Table 9: Example one-half reduction matrix design on time points for a product with 2 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

T = Sample tested

Table 10: Example one-third reduction matrix design on time points for a product with 2 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

T = Sample tested

Additional examples of matrixing design for a product with 3 strengths (50 mg, 75 mg, and 100 mg) and 3 container sizes (15 mL, 100 mL, and 500 mL) are provided in Table 11 and Table 12. Table 11 illustrates a matrixing design on time points only, whereas Table 12 illustrates a matrixing design on both time points and factors. In Table 11, all combinations of batch, strength, and container size are included. The time points (months) used in the examples presented in Table 11 and Table 12 are listed in Table 13.

Table 11: Examples of matrixing on time points for a product with 3 strengths and 3 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 12: Examples of matrixing on time points and factors for a product with 3 strengths and 3 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	

Table 13: Time points (months) for examples in Table 11 and Table 12

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 being 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.

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 the use of supportive stability data.

A study design that uses matrixing 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 would still be performed 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, time points, 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., 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 the 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 CQAs 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, they should be 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 and illustrated in Table 14 and Table 15. 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 time points 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 the 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, and/or
- Demonstrates how different storage conditions may impact stability and that the worst-case storage conditions relevant to the drug substance or drug product are selected for evaluation, and/or
- Demonstrates that specific time points are not meaningful for assessment of trends.

Example 1: Reduction from the Primary Stability Study to the Commitment Study that Confirms Shelf Life for a 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*) may include historical data and accumulated knowledge supporting:

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

Table 14: Example of a protocol design for primary stability studies

Storage Condition	Time point (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					

RH = relative humidity

A: Release testing

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

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

Table 15: Example of a protocol design for commitment stability studies to confirm shelf life

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

RH = relative humidity

A: Release Testing

B: Appearance, Assay, Degradation Products, Dissolution

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 is predictable, then a worst-case approach could be proposed to support a reduction in 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* and *Annex 2 – Stability Modelling* 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 a 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 appropriateness of the statistical method should be justified with respect to consideration for data that may not be balanced due to a reduced design. 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 (*Annex 1, Section A1-3.3 – Knowledge and Risk Based Protocol Reductions*), the same statistical principles may be applied.

ANNEX 2: STABILITY MODELLING

A2-1 Introduction

General information on the 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 – Protocol Design for Formal Stability Studies* (refer to Table 1, Section 3.2.1 and Table 2, Section 3.2.2) and *Section 13 – Data Evaluation*, respectively. When limited long-term data are available, *Section 13.3.1 – Extrapolation for Synthetic Chemical Entities* may be referenced to establish an initial re-test period or shelf life of a drug substance or drug product for synthetics. Enhanced stability modelling approaches could also be considered using the principles in *Annex 2, Section A2-3 – Enhanced Stability Modelling*. 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 *Annex 2, Section A2-3 – Enhanced Stability Modelling* or using the specific basic extrapolation principles (refer to *Section 13.3.2 – Extrapolation for 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 to propose an initial re-test period or shelf life. While extrapolation and enhanced stability models may be used to predict the stability profile at submission, these approaches should be considered as part of a comprehensive stability programme and are not intended to replace long-term stability studies.

This Annex is structured in two parts; the first provides examples for the basic stability models and related statistical tools commonly used to establish a re-test period or shelf life (*Annex 2, Section A2-2 – Statistical Evaluation of Stability Data from Single or Multi-Factor Study Designs*). This includes tools to assess the variability between batches for single-factor and multi-factor, full design studies, and a decision tree-based tool for synthetic chemical entities to extrapolate data beyond the period covered by long-term stability data. The second part describes enhanced stability models for well-characterised molecules that may be based on the empirical fit of stability data to kinetic functions (e.g., Arrhenius equation-derived thermokinetic models) or incorporating prior knowledge into data evaluation (e.g., Bayesian-based statistical approach; *Annex 2, Section A2-3 – Enhanced Stability Modelling*).

Basic and enhanced stability models are distinguished by their relative complexity. Enhanced stability modelling (refer to *Annex 2, Section A2-3 – Enhanced Stability Modelling*) refers to the application of advanced mathematical, kinetic, and statistical approaches to evaluate the stability of drug substances and drug products. These approaches extend beyond the simple, frequentist statistical tools traditionally used in basic stability modelling. Basic models

typically do not incorporate mechanistic understanding of degradation pathways. Enhanced models are typically applied to well-characterised products, including those with a high level of product and process understanding as defined in ICH Q8, and may incorporate product-specific prior knowledge as well as information from structurally and functionally related ("analogous") molecules.

As a general principle, the least complex statistical model that best describes the data is recommended. Depending on the model and its context of use, the core study design elements that should be considered as part of any prospective stability modelling strategy include:

1. Purpose of the model.
2. 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 prediction, limitations, and assessing model robustness.
8. Model validation.
9. 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).
10. Model verification with real-time data, plans for ongoing model monitoring, and lifecycle considerations, as needed.
11. Risk management strategy if differences are observed between the predicted shelf life and actual shelf life based on confirmatory data.

A model's usage can be expected to be constrained by the modelling method, input data, or output predictions, and conditions evaluated, 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 PQS after successful validation and verification.

A2-2 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 individual batches used for a single product and multi-factors include different fill volumes, concentrations, and container dimensions to set the re-test period or shelf life when the stability protocol is not reduced by bracketing or matrixing (32). 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 are expected to meet the criteria outlined in *Section 3 – Protocol Design for Formal Stability Studies* and elsewhere in this guideline. Useful references for the statistical approaches demonstrated in this guideline can be found in *Section 17 – References* (26–27, 30, 33). Data evaluation for reduced study designs is described in *Annex 1 – Reduced Stability Protocol Design* and *Section 13 – Data Evaluation*.

A2-2.1 Evaluation of 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 within a range of interest. The guideline describes how, for synthetic chemical entities, the available long-term stability data may be extrapolated to establish a shelf life using a decision tree approach (refer to *Annex 2, Section A2-2.4 – Extrapolation for Synthetic Chemical Entities Based on the Decision Tree*). 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 may be used to establish the re-test period or shelf life. Combining multiple batches is discussed in *Annex 2, Section A2-2.2 – Linear Models to Assess Stability Profile Using Multiple Batches* and *Section 13.2.2 – Combining Data from Multiple Batches*.

For a single batch (single-factor studies), linear regression using a 95% confidence limit may be conducted. Analyses of a quantitative attribute for a single batch can be performed by determining the earliest time at which the 95% confidence limit intersects the proposed acceptance criterion, and the shelf life should be based on the batch with the confidence limit that crosses this threshold first.

For an attribute known to decrease with time, the lower one-sided 95% confidence limit should be compared to the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95% confidence limit should be compared to the acceptance criterion. For attributes with upper and lower acceptance criteria, a two-sided 95% confidence limit is recommended.

A2-2.2 Linear Models to Assess Stability Profile Using Multiple Batches

When stability data for more than a single batch are assessed, the data evaluation may use a linear model to evaluate the attribute stability profile at stated storage conditions and support a re-test period or shelf life.

A linear model (fixed effects or mixed effects model) may be applied to stability data, with appropriate statistical limits to establish the maximum re-test period or shelf life that may be claimed.

The accuracy and precision of the analysis are determined by the number of batches suitable for the analysis, and the number and spread of data points within each time-course study. Applicants are advised that there is an inherent risk of inaccurate representation of the stability profiles of future production batches dependent on the number and representativeness of batches included in the analysis. Therefore, these aspects should be considered in the study design.

The minimum data set is discussed in the guideline (refer to *Section 3 – Protocol Design for Formal Stability Studies*). The applicant should justify the statistical limits used (for example, confidence limits, tolerance intervals, or prediction intervals) according to the intended purpose and model type.

Two model types are outlined below for the linear regression evaluation of stability data to establish a 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, Section A2-2.2.1 – Fixed Effects Model*) or as a random variable (refer to *Annex 2,*

Section A2-2.2.2 – Mixed Effects Model) and whether the other variables are fixed or random. The choice of model generally depends on the target of inference, the number of batches used for the evaluation, and the context of use for the model.

A2-2.2.1 Fixed Effects Model

A fixed effects model may be chosen when limited batches are available (e.g., 3 primary stability batches). The model may be specified to include time, batch, and batch-by-time interaction as fixed effects. Fixed effects models provide inference limited to the observed batches and cannot ensure the quality of future batches. However, the model accounts for the worst-case stability behaviour among the observed batches and is a statistically meaningful approach with a small number of batches.

The significance level should be selected and justified based on the totality of the study design, including the number of batches. 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. When the available number of batches and/or testing time points is larger, a more stringent significance level (i.e., lower p-value) should be considered to reduce the risk of identifying differences that are not practically meaningful.

For regression lines, 95% confidence limits are generally applied, and these limits may be one-sided or two-sided. This depends on the acceptance criteria and whether the attribute is known to be increasing or decreasing.

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

A2-2.2.2 Mixed Effects Model

A mixed effects model may be chosen when multiple batches (e.g., five or more) 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.

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). The larger number of batches provides greater assurance that the inferred stability profile is representative of future batches manufactured using the same process.

The statistical limits used, which may include confidence limits, tolerance intervals, a prediction interval, or other tools, should be justified with a discussion on limitations of the chosen approach. As one possible example, a tolerance interval-based approach using the linear mixed effects model may be selected and applied to determine an extended shelf life beyond the period covered by long-term data, with the appropriate justification and a discussion on limitations.

A2-2.3 Linear Models to Assess Stability Profile Using Multiple Factors and Factor Combinations

Analysis of covariance 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 evaluated for the estimation of a single shelf life (refer to *Section 13.2.5 – 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 the container is taken into account in each measure as comparisons are made to the initial time point analysed prior to packaging.

The decision whether data from different factors or factor combinations may be combined should incorporate subject matter knowledge concerning factors that may influence the stability profile, together with appropriate model diagnostics. Relevant considerations may include statistical significance tests in an appropriate order, goodness-of-fit statistics, analysis of residuals, estimates of intercepts and slopes with their uncertainty, variance components, and the magnitude of heterogeneity among factors or factor combinations. Statistical significance alone should not determine whether data are combined. The assessment should consider whether any observed differences are meaningful for estimation of shelf life.

When statistical significance tests are used to justify combining data, the tests should be specified to determine whether there are meaningful differences among factors and factor combinations. If the tests show that the data from different factor combinations can be combined, the shelf life can be estimated according to the procedures described for a single batch or multiple batches (refer to *Annex 2, Section A2-2.1 – Evaluation of Stability Data in Single-Factor, Full Design Studies Using Linear Regression Models* and/or *Annex 2, Section A2-2.2 – Linear Models to Assess Stability Profile Using Multiple Batches*) using the combined data.

A2-2.4 Extrapolation for Synthetic Chemical Entities Based on the Decision Tree

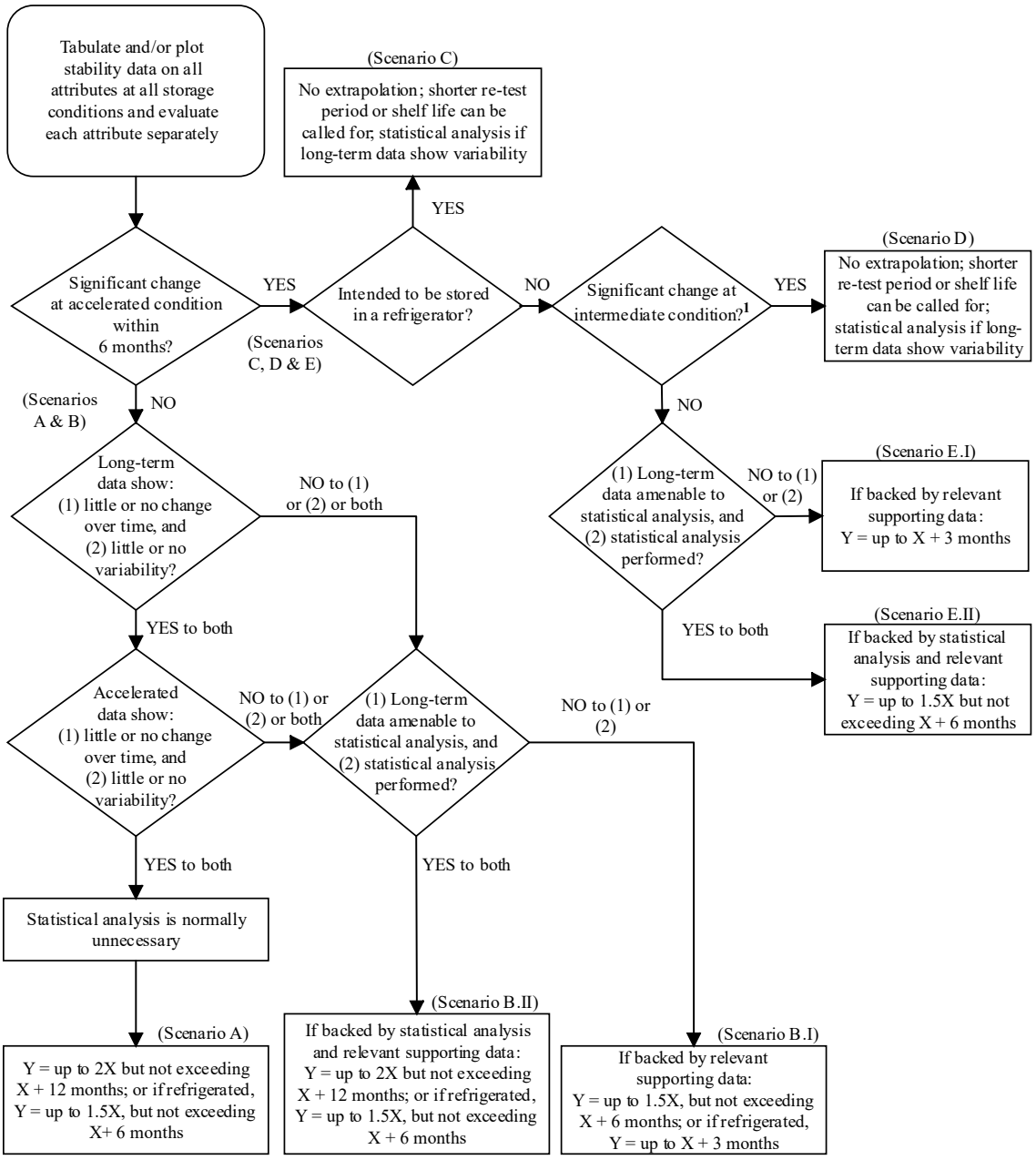
A systematic approach using a decision tree (Figure 4) is provided as a tool for appropriate data extrapolation beyond the period covered by long-term stability data.

The decision tree is intended to apply to synthetic chemical entities that are stored long-term at room temperature or under 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).

While the decision-tree approach may support limited extrapolation, enhanced modelling methodologies may provide an alternative approach with greater potential for extrapolation beyond these stated limits (refer to *Annex 2, Section A2-3 – Enhanced Stability Modelling*).

The decision tree is applicable when 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. This generally requires that the available long-term stability data be amenable to statistical analysis, taking into consideration factors such as the number and frequency of data time points. 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 – Storage Statements in 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)



X = period covered by long-term data; Y = proposed re-test period or shelf life

[1] When no intermediate condition is defined for the climatic zone, refer to Scenario D.

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 progress through the trends and variability of the long-term data. The circumstances are delineated under which extrapolation of the re-test period or shelf life beyond the period covered by long-term data can be appropriate. Relevant supporting data may include satisfactory long-term data from development batches that are (1) made with a comparable formulation, (2) manufactured on a different scale, or (3) packaged in a container closure system similar to that of the primary stability batches.

For a synthetic chemical drug substance, a significant change is when an attribute exceeds specification at the accelerated condition within 6 months or at the long-term storage condition within the intended shelf life or re-test period.

For a 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, performance tests (e.g., dose delivery per actuation).

Additionally, for certain dosage forms:

3. Failure to meet specification for pH.
4. Failure to meet specification for dissolution testing.
5. 5% loss in water from its initial value for aqueous-based products stored in semi-permeable containers (refer to *Section 7.2 – Considerations for Products Intended to be Stored at Room Temperature Conditions*).

With respect to physical attribute changes, the following can be expected to occur at the accelerated condition and would not be considered a 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 a 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, if applicable (refer to *Section 7.2 – Considerations for Products Intended to be Stored at Room Temperature Conditions*).

The following subsections describe the decision tree approach in Figure 4 and the scenarios illustrated.

A2-2.4.1 No Significant Change at Accelerated Conditions (Scenarios A and B)

Based on the decision tree, when there is no significant change at the accelerated condition within 6 months, 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.

For **Scenario A**, where the long-term data and accelerated data for an attribute show little or no change over time and little or no observed 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.

For **Scenario B**, the decision tree approach considers the significance of change over time under accelerated and long-term storage conditions and method variability. 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.

For **Scenario B.I**, 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 refrigerated storage, the proposed re-test period or shelf life can be up to 3 months beyond the period covered by long-term data. 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.

For **Scenario B.II**, 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 two times, but NMT 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.

A2-2.4.2 Significant Change at Accelerated Conditions (Scenarios C, D and E)

Where significant change occurs at the accelerated condition within 6 months, the re-test period or shelf life would depend on the storage condition (room temperature or refrigerated) and whether stability data at an intermediate condition are available.

For **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.

For **Scenario D**, for room temperature storage, where significant change occurs at both the 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.

When there is a significant change at the accelerated condition and no intermediate condition is defined for the climatic zone (refer to Table 4, Section 7.2), extrapolation is generally not considered appropriate given the absence of intermediate condition data. However, depending on whether the data for the attribute are amenable to statistical analysis and statistical analysis is performed, an extrapolation beyond the period covered by long-term data may be proposed. The extrapolation should not be longer than what is proposed in scenario E.II described below.

For **Scenario E**, for room temperature storage, if there is significant change at the 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.

For **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. 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.

For **Scenario E.II**, if a 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 when backed by statistical analysis and relevant supporting data.

A2-3 Enhanced Stability Modelling

This section provides scientific and regulatory considerations for enhanced stability model development, validation, verification, and maintenance over the 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.

Model credibility is built incrementally using a comprehensive approach that includes model development, model validation, and model verification. A comprehensive approach should include evaluation of both analytical and statistical approaches.

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 include 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 *Annex 2, Section A2-2 – Statistical Evaluation of Stability Data from Single or Multi-Factor Study Designs*).

A2-3.1 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 a re-test period or shelf life. These concepts are expanded in the subsequent sections of this Annex. A stability model used to set a commercial re-test period or shelf life would be typically 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 is 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 programme 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. Refer to *Section 2 – Development Stability Studies under Stress and Forced Degradation Conditions* and *Section 3 – Protocol Design for Formal Stability Studies* 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 initial 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.

A2-3.2 Model Development

A2-3.2.1 Choice of Model Type

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.
- The fit of stability data at the recommended storage condition to a kinetic formula.
- Thermokinetic reactions with the fit of the 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 an accurate prediction or inference of a quality attribute stability profile. The level of detail expected to demonstrate accuracy is generally proportional to model impact, within the context of use (refer to ICH Q8–10). Prior to further development of in-house models, the applicant is expected to perform code verification and calculation verification.

Model appropriateness and suitability should be evaluated on a case-by-case basis. For example, 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; whereas molecules with more complex degradation pathways such as a biological drug substance or drug product may be less amenable to modelling by the humidity modified Arrhenius equation using accelerated condition data.

Enhanced stability models can fall under two broad classes: (1) those that utilise prior knowledge only from 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.

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 stress conditions as described in *Section 7 – Storage Conditions*.

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.

A2-3.2.2 Selection of Critical Quality Attributes (CQAs) for Stability Modelling

The selection of CQAs for modelling follows the same principles described in the core guideline for protocol design (refer to *Section 3.3 – Critical Quality Attributes [CQAs]*) and is adapted to the purpose of stability model development.

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.

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 approach the upper or lower bounds most likely in the attribute specification over the storage period (ICH Q6A and ICH Q6B) and are shelf life limiting. The selection of stability-indicating CQAs used in models, from those that define the stability profile (refer to *Section 3 – Protocol Design for Formal Stability Studies*) should be justified, and the impact of an attribute (not part of the model) changing unexpectedly should be considered as part of risk management (refer to *Section 3.7 – Risk Management, and Annex 2, Section A2-3.5 Risk Management and Model Lifecycle Considerations*).

A2-3.2.3 Selection of Data and Parameters to Construct a Stability Model

The data used to build a stability model are typically based on stability testing results from the long-term primary and production 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 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 system, 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 the 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.

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, especially when prior knowledge from analogous molecules is used in a stability model. 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 the final, simplest model that provides the best prediction accuracy (least difference between the predicted value and the actual experimental value).

A2-3.3 Evaluation of Data for Stability Modelling

The modelling 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 drug-specific stability data evaluated using linear regression and for the combining of batches for a drug substance or drug product are outlined in *Section 13 – Data Evaluation* of the core guideline and *Annex 2, Section A2-2 – Statistical Evaluation of Stability Data from Single or Multi-Factor Study Designs*. The following sections in this Annex provide additional options when using enhanced stability models for the purpose of extrapolating the stability profile past the available data at the recommended storage conditions. The uncertainty in the predicted profile over time is typically addressed using justified statistical intervals to ensure that the true profile or future data or a defined proportion of the data lies 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, as part of model validation, to avoid overfitting the kinetic function to the data when the model incorporates the variability, thereby reducing the accuracy of prediction.

Other models may use prior knowledge data that is evaluated using, for example, Bayesian statistics as an alternative to conventional Frequentist statistics. The Bayesian method derives a predictive posterior distribution for the quality attributes 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 validation and verification 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 re-test period or shelf life prediction, applicants should provide a risk-based and scientifically justified duration for the proposed re-test period or shelf life when using enhanced approaches. When utilising enhanced stability modelling to support a re-test period or shelf life, the extent of prediction should be based on scientific understanding, risk assessment (including the 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 the statistical approach.

A2-3.4 Stability 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 validation and verification should reflect both analytical and statistical considerations.

Stability Model Validation: 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*).

In validating a model, 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 (25–30, 32–33). For example, by applying the model to a known, full stability data set, for which the last time point result(s) has not been included, the value for that last time point 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 time point may not be sufficient.

The quality of the model should be demonstrated by evaluating the error between the model prediction and the data used to build the model. The fit of the data to the prediction should be demonstrated as an indicator of model quality and to reduce bias (over or under-fitting). The statistical tools used can depend on the type of stability model being developed. Approaches may include goodness-of-fit and internal cross-validation. For example, when a model uses

accelerated condition data for a synthetic product and the degradation kinetics obey a modified Arrhenius equation, the fit of the experimental data to the model theoretical output at different accelerated storage conditions could be assessed.

To test model accuracy and ensure that the model behaves as expected, additional validation approaches should also be performed using external (independent) data sets that were not used to develop the model. Models that are built using accelerated condition data may include the available long-term stability data as part of the model validation.

Stability Model Verification*:* 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 ongoing verification to confirm that the model predictions remain accurate and do not impact the initially predicted shelf life.

A2-3.5 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 a 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 are evaluated to ensure patient safety. The stability-indicating CQAs are also selected, and the stability profile defined. Particular note should be taken in discussing the risk presented by any use of “analogous molecules” that refers to differences between molecules that may impact their stability profile and the extent to which the knowledge is transferable for use in the stability model.

A stability model, depending on the model type, attributes modelled, and intended purpose, may require updating through the 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 that are obtained support the identified attribute trend. A lifecycle approach could include updating the regulatory authorities with additional verification data and updating the initially predicted shelf life if appropriate.

The post-approval and ongoing monitoring/trending of new drug substance or drug product stability data should be managed by the manufacturer's PQS. The PQS should be capable of detecting and managing any unexpected changes in stability trend and out-of-specification results with appropriate CAPA as described in ICH Q10, relevant to any stability model being used to establish a 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 (e.g., re-evaluation of the initially predicted shelf life).

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 include somatic cell therapy, gene therapies, and tissue-engineered products that have been substantially manipulated and/or perform a different function in the recipient than in the donor (34). ATMPs have several unique characteristics that should be reflected in the design and execution of the stability programme.

In some circumstances, the mechanism of action may be complex with multiple targets and/or potentially multiple modes of action and, as such, the CQAs are not always fully understood. For these reasons, some of the principles outlined in the core guideline may not be applicable

to ATMPs (e.g., accelerated stability studies may not be predictive of the actual degradation profiles during storage but may provide supportive information).

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 as a single batch that may even be sufficient for the entire clinical study, leading to challenges in conducting stability studies using multiple production batches.

The standard approach for establishing shelf life for ATMPs should be based on real-time stability studies, as there may be limited prior knowledge available to support model-based approaches to the stability assessment. Stability design for an ATMP should be based on a science- and risk-based approach due to challenges, such as complex mechanisms of action, limited material from patient-specific small batches, inherent assay and batch variability, and manufacturing strategies (e.g., decentralised manufacturing).

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 – Protocol Design for Formal Stability Studies* to *Section 14 – Storage Statements in Labelling* should serve as the basis for designing a stability programme 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 are discussed under *Section 12 – Reference Materials, Novel Excipients, and Adjuvants*.

The document covers the generation and submission of stability data for products containing biological drug substances such as autologous and allogeneic cell-based products (e.g., mesenchymal stromal cells (MSCs)), Islet cells, T-cells, NK cells, cell-derived products (e.g., secretomes), 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, genetically modified viral, and 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 and vectors used *ex vivo* to modify cells (e.g., retroviruses, adeno-associated viral and other nucleic acid-based vectors). This Annex is also applicable to viral and bacterial banks used in the manufacture of viral and bacterial vectors.

Due to the diversity of ATMP products, the stability programme 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 and storage conditions. For example, the primary stability protocol for a vector-based gene therapy product for treating larger patient populations may be different from that for a patient-specific cell-based gene therapy product.

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, and the ATMP stability study design should be based on process and product knowledge. Stability testing frequency should follow the recommended testing frequency as detailed in *Section 6 – Testing Frequency*. When the patient-specific ATMPs are stored before use 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 of the product and process. For cryopreserved cell therapy products, reduced testing frequencies could be justified based on developmental data and prior knowledge. Stability studies for ATMPs may be performed using a container closure system differing from the one proposed for the commercial product, when justified and supported by data showing suitability of the alternative container closure system.

When ATMPs are stored for a short period of time (e.g., stored for a few hours at 2–8°C) after manufacture, the storage period should be based on results from primary stability studies. A primary stability study for such products would generally include a minimum of two stability test points after a release test using representative batches. Under these circumstances, recommendations for periodic stability testing as described in the core guidance (*Section 3 – Protocol Design for Formal Stability Studies*) will not be necessary. The number of lots needed to confirm product stability in such cases may be more than the minimal number of lots required to assess stability (*Section 3 – Protocol Design for Formal Stability Studies*), depending on product variability, and should be based on a risk evaluation and justified based on empirical data.

Some ATMPs are more sensitive to shear forces during shipping and transportation. Shipping stability studies should be performed at various stages in the manufacturing process, starting from the procurement, storage, and shipping of patient-derived or donor-derived cell-based starting materials to drug substance and/or drug product. Typical shipping stability study parameters should include an evaluation of stability-indicating CQAs in addition to temperature maintenance and CCIT during and after shipping. Shipping stability studies for ATMPs may be performed using surrogate materials when justified.

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.

A3-3.1 Selection of Analytical Procedures and Acceptance Criteria

Selection of analytical procedures and acceptance criteria is detailed in the core guideline (refer to *Section 3.4 – Specifications*). Uncertainty surrounding stability-indicating 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 the stability of ATMPs. However, assessing the 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 *in vivo* biological activity, and the inherent variability in cell- and tissue-based products 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 confirmed. When one assay is not sufficient to fully evaluate all the different biological activities, 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 (e.g., potency). For gene therapy products, this may be evaluated through tests such as transduction, infectivity, gene expression, and/or activity of the expressed product, as relevant.

The purity of the ATMP should be assessed to ensure that the storage period and conditions do not lead to an increase in the levels of impurities beyond the demonstrated acceptable range obtained from product lots used to establish safety and efficacy. Impurities in ATMPs result from either the manufacturing process or are product-related, where the latter may include, for instance, degraded viral particles or cells. 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, the levels of product-related impurities in an ATMP should be quantitated, and the acceptable stability limits should be justified. Stability-indicating quality attributes related to residual product-related 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 quality attributes 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 (refer to *Section 3.4 – Specifications*) for assessing the stability of ATMPs, the following are examples for product-specific stability considerations that should be evaluated as part of the stability assessment (additional product-specific parameters are recommended to be tested as applicable to the product type):

- For live cell-based products that are stored frozen, it is important to consider the impact of the freeze-thaw process on cell viability and potency 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 viral vector-based products, product CQAs such as changes to potency, total particle number, or a measure of titre (e.g., protein expression and/or genome copy

number), infectious particle number, and viral genome titre should be considered in the stability studies, as appropriate for the viral vector under study.

- For viral vectors that are used to further modify cells *ex vivo*, potency, titre, and other stability-indicating CQAs should normally be considered in stability studies.
- For bacteria-based products, the viability, bacteria count, and plasmid copy number (if applicable) should be considered.
- For recombinant nucleic acid (DNA or RNA-based) ATMP products, stability determination may also include an assessment of sequence integrity, structural integrity (e.g., supercoiling), and quantity (strength), in addition to other CQAs. When formulated with a delivery system (e.g., lipid nanoparticle), stability considerations should include other CQAs to ensure optimal delivery and efficacy are maintained. Stability-indicating CQAs may include encapsulation, purity, particle size, polydispersity, organisation, content (e.g., lipid components), and assurance of functionality.
- For tissue-engineered products, physicochemical and functional CQAs should be evaluated as 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 drug substances that cannot be fully characterised or drug 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 cell identity based on phenotype; percent (%) transduced cells in case of an *ex vivo* modified cell-based 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 in line with the principles outlined in ICH Q6B. When justified, shelf life specifications may differ from the release specification.

A3-3.2 Selection of Study Conditions

Recommendations for the selection of study conditions are outlined in the core guideline (refer to *Section 3 – Protocol Design for Formal Stability Studies* to *Section 7 – Storage Conditions*). It is expected that the stability studies for ATMPs include real-time storage and in-use period conditions.

Accelerated or stress testing may not provide direct information to support a shelf life; however, testing under accelerated and stress conditions may be appropriate for ATMPs for the following reasons. Accelerated studies may be utilised to gain knowledge of the stability profile. Testing under these conditions helps 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 stress 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, stress, and forced degradation conditions should be carefully selected based on a risk assessment and worst-case conditions relevant to an ATMP's shipping, handling, and storage.

A3-3.3 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 a risk evaluation, an alternative number of stability batches may be justified. The risk to an accurate determination of the predicted shelf life of an ATMP will depend on various factors, including the assay limitations and variability in 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 Batches*), the manufacturing scale of the primary stability batches for ATMPs may differ from that of the production batch, provided the primary stability batch scale change does not represent a significant risk to the prediction of stability of the production batches.

When primary batches are not production batches, a post-approval commitment should be included to confirm stability. Shelf life of patient-specific cell-based ATMPs should be determined 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 may be acceptable. When feasible, stability data from patient-derived material should also be taken into consideration to establish a shelf life. When patient-derived material is only available in limited quantities to perform the recommended stability studies in accordance with the stability protocol, the principles of bracketing (refer to *Annex 1 – Reduced Stability Protocol Design*) may be applied to ATMPs.

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 some 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 hold time, a risk assessment should be performed to determine and justify the need and extent of hold time stability studies. Some ATMP manufacturing processes 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

In general, assessment of stability of starting materials during their storage and shipping should follow the recommendations detailed in this guideline for ATMPs and should follow a risk-based approach to determining their stability. Some ATMPs may be manufactured in small

quantities, and the stability protocol design should take into consideration the amount of available material, where a reduced protocol could be justified.

The stability protocol should take into consideration that the stability of ATMPs may be affected by the quality of starting materials and viral vectors, and the stability assessment should consider the impact of starting materials for cell therapy products (e.g., allogeneic, 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 cell-based starting materials (e.g., donor cells) should be assessed during their storage and shipping. Stability of starting materials used to manufacture gene therapy vectors (e.g., plasmids, virus banks used to make vectors) should also be assessed based on risk.

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-indicating 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, the 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 stored under defined storage conditions should be demonstrated to verify that the thawed cells have survived the preservation process and retain their CQAs within acceptable limits, consistent with the recommendations outlined in ICH Q5D, and cell viability should be assessed to assure stability. A stability protocol for monitoring of banked cells should be provided in the submission. Stability-indicating CQAs 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 the initial shelf life beyond long-term data at submission.

The stability of viral banks that are used either for 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.

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 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 the intended use of the viral bank. Infectious titre and other potency-related CQAs can be stability-indicating, depending on the intended use of the viral bank, and should be monitored.

A3-5 Establishment of Shelf Life of an ATMP

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. Since the accelerated stability studies only provide 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 long-term stability data from production batches are not available for ATMPs, stability data from developmental batches and prior knowledge from similar products may be used as supporting data to justify setting an initial stability period, with a concurrent testing strategy built into the stability protocol. For developmental batches, analytical comparability should be demonstrated and the storage conditions, including the composition of formulation buffers, should be the same as those of the production batches (in line with recommendations outlined in *Annex 3, Section A3-3.3 – Selection of Batches*).

A minimum of 6 months stability data from material manufactured using the commercial process and the proposed container closure system, or material representative of the commercial manufacturing process and container closure, should be included at the time of submission. The shelf life may be extended beyond the initial 6-month period when additional stability data become 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.

The use of prior knowledge, extrapolation, and modelling (as described in *Annex 2 – Stability Modelling*) to support initial shelf life estimation of an ATMP may be considered in consultation with regulatory authorities when sufficient prior knowledge is available and scientifically justified in line with the principles laid out in *Annex 2 – Stability Modelling*.

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 – Protocol Design for Formal Stability Studies* of the core guidance. When intermediates used in the manufacture of cell-based products and viral vectors are stored, they should also be assessed for their stability under a pre-specified stability protocol and a shelf life established based on real-time stability information.