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BIOLOGICAL MEDICINES STABILITY GUIDELINE

This guideline is intended to give guidance to applicants regarding the type of stability that should be provided in support of the shelf-life of the biological medicines. It represents SAHPRA current thinking on the safety, quality and efficacy of the biological medicines. This guideline is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information that may be deemed necessary to establish the safety, quality and efficacy of a biological medicine in keeping with the knowledge that is current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. SAHPRA is committed to ensure that, all registered medicines are of the required quality, safety and efficacy. It is therefore important that applicants adhere to all the administrative requirements to avoid delays in the processing and evaluation of applications. This guideline is adopted from ICH Q5C guideline with minor modification. Guidelines and application forms are available from the office of the CEO and on SAHPRA website.

Document History

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Contents

GLOSSARY

The following terms, which have been in general use, and their definitions, are provided to facilitate interpretation of the guideline.

Abbreviation/ Term	Meaning
Bracketing	The design of a stability schedule so that at any time point, only the samples at the extremes, for example of container size and/or dosage strengths, are tested. The design assumes that those at the extremes represent the stability of the intermediate samples. Where a range of dosage strengths are to be tested, bracketing designs are particularly applicable if the strengths are very closely related in composition. Where a range of sizes of immediate containers is to be evaluated, bracketing designs may be applicable if the composition of the material from which the containers are made, and the type of closure, are the same throughout the range.
Degradation Product	A molecule resulting from a change in the active biological substance (bulk material) brought about over time. For the purpose of stability testing of the products described in this guideline, such changes could occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis). For biological products some degradation products may be active.
Dosage Form/Preparation	A product type, for example solution, injection etc. that contains an active biological substance generally but not necessarily, in association with inactive ingredients.
Excipient	Anything other than the active biological substance in the dosage form.
Final Product (FP)	The dosage form in the final immediate packaging intended for marketing.
Impurity	Any component of the active biological substance (bulk material) or Final product (final container product) which is not the chemical entity defined as the active biological substance, an excipient, or other additives to the Final product.
Intermediate	For biological products, a material produced during a manufacturing process which is not the active biological substance or the Final product but whose manufacture is critical to the successful production of the active biological substance or the Final product. Generally, an intermediate will be quantifiable and specifications will be established to determine the successful completion of the manufacturing step prior to continuation of the manufacturing process. This includes material which may undergo further molecular modification or be held for an extended period prior to further processing.
Manufacturing Scale Production	Manufacture at the scale typically encountered in a facility intended for product production for marketing.
Matrixing	The statistical design of a stability schedule such that only a fraction of the total number of samples is tested at any specific sampling point. At a subsequent

	sampling point, different sets of samples of the total number, would again be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure, and possibly in some cases, different container/closure systems. Matrixing permits reduced testing when more than one variable is being evaluated. Thus, the design of the matrix will be dictated by the factors that need to be covered and evaluated. The potential complexity precludes inclusion of specific details and examples. It is essential that, in each case, all batches are tested initially, and at the end, of the long-term testing programme.
Pilot-Plant Scale	The production of the active biological substance or final product by a procedure fully representative of and simulating that to be applied at manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

1. INTRODUCTION

The guidance stated in the ICH harmonized tripartite guideline "Stability Testing of New Drug Substances and Products" (27 October 1993) applies in general to biological products. However, biological products have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. The biological products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. Therefore, in order to ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary.

The evaluation of stability may necessitate complex analytical procedures/ methodologies. Where applicable, Assays for biological activity, should be part of the pivotal stability studies. Appropriate physicochemical, biochemical and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program whenever purity and molecular characteristics of the product permit use of these methodologies.

With the above concerns in mind, the applicant should develop the proper supporting stability data for a biological product and consider many external conditions which can affect the product's potency, purity and quality. Furthermore, primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product.

1.1 Purpose

This guideline is intended to give guidance to applicants regarding the type of stability that should be provided in support of the shelf-life of the biological medicines. It represents SAHPRA current thinking on the safety, quality and efficacy of the biological medicines.

1.2. Scope

This guideline is applicable to well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumour necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well- characterized proteins or polypeptides. For guidance regarding the stability requirements of conventional vaccines, applicants should consult the WHO "Guidelines on stability evaluation of vaccines" and relevant TRS. This guideline also does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components.

2. LEGAL PROVISION

Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended and the relevant Regulations.

3 SELECTIONS OF BATCHES

3.1. Active Biological Substance (Bulk Material)

3.1.1 Where bulk material is to be stored after being manufactured but before formulation and final manufacturing, stability data should be provided on at least 3 batches for which manufacture, and storage are representative of the manufacturing scale of production. A minimum of 6 months' stability data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested.

3.1.2 For active biological substances with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Data from pilot-plant scale batches of drug substance produced at a reduced scale of fermentation and purification may be provided at the time the dossier is submitted to SAHPRA together with a commitment to place the first 3 manufacturing scale batches into the long-term stability program after approval.

3.1.3 The quality of the batches of active biological substance placed into the stability program should be a representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made at manufacturing scale. In addition, the active biological substance (bulk material) made at pilot-plant scale should be produced by a process and stored under conditions representative of that used for the manufacturing scale.

3.1.4 The active biological substance entered into the stability program should be stored in containers which properly represent the actual holding containers used during manufacture. Containers of reduced size may be acceptable for drug substance stability testing provided that they are constructed of the same material and use the same type of container/closure system that is intended to be used during manufacture.

3.2. Intermediates

3.2.1 During manufacture of biotechnological/biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that assure their stability within the bounds of the developed process. While the use of pilot-plant scale data is permissible, the manufacturer should establish the suitability of such data using the manufacturing scale process.

3.3. Final Product

3.3.1. Stability information should be provided on at least 3 batches of final product representative of that which will be used at manufacturing scale. Where possible, batches of final product included in stability testing should be derived from different batches of bulk material. A minimum of 12 months' data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested.

3.3.2. For Final products with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Final Product shelf life will be based upon the actual data submitted in support of the application. Since shelf life is based upon the real- time/real-temperature data submitted for review, continuous updates of the initial stability data should occur during the review and evaluation process. The quality of the final product placed on stability studies should be representative of the quality of the material used in the preclinical and clinical studies.

3.3.3. Data from pilot-plant scale batches of final product may be provided at the time the dossier is submitted to SAHPRA with a commitment to place the first 3 manufacturing scale batches into the

long-term stability program after approval. Where pilot-plant scale batches were submitted to establish the shelf life for a product and, in the event that product produced at manufacturing scale does not meet those long-term stability specifications throughout the shelf life period or is not representative of the material used in preclinical and clinical studies, the applicant should notify the appropriate regulatory authorities to determine a suitable course of action.

3.4. Sample Selection

3.4.1. Where one product is distributed in batches differing in fill volume (e.g., 1ml, 2 ml, or 10 ml), units (e.g., 10 units, 20 units, or 50 units), or mass (e.g., 1 mg, 2 mg, or 5 mg) samples to be entered into the stability program may be selected on the basis of a matrix system and/or by bracketing (for more information refer to ICH Q1D guideline).

3.4.2. Matrixing, i.e., the statistical design of a stability study in which different fractions of samples are tested at different sampling points, should only be applied when appropriate documentation is provided that confirms that the stability of the samples tested represents the stability of all samples. 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 closure and possibly, in some cases, different container/closure systems.

Matrixing should not be applied to samples with differences that may affect stability, such as different strengths and different containers/closures, where it cannot be confirmed that the products respond similarly under storage conditions.

3.4.3. Where the same strength and exact container/closure system is used for 3 or more fill contents, the manufacturer may elect to place only the smallest and largest container size into the stability program, i.e., bracketing. The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples is represented by those at the extremes. In certain cases, data may be needed to demonstrate that all samples are properly represented by data collected for the extremes.

4. STABILITY-INDICATING PROFILE

There is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. The manufacturer must propose a stability-indicating profile that provides assurance that changes in the identity, purity and potency of the product will be detected.

At the time of submission, applicants should have validated the methods that comprise the stability-Indicating profile and the data should be available for review. The determination of which tests should be included will be product specific. The items emphasized in the following subsections are not intended to be all-inclusive but represent product characteristics that should typically be documented to adequately demonstrate product stability.

4.1. Protocol

4.1.1 The dossier accompanying the application for product registration should include a detailed protocol for the assessment of the stability of both active biological substance and Final product in support of the proposed storage conditions and shelf life.

4.1.2 The protocol should include all necessary information which demonstrates the stability of the biotechnological/biological product throughout the proposed shelf-life period including, for example, well-defined specifications and test intervals.

4.2. Potency

4.2.1 When the intended use of a product is linked to a definable and measurable biological activity, testing for potency should be part of the stability studies. For the purpose of stability testing of the products described in this guideline, potency is the specific ability or capacity of a product to achieve its intended effect. It is based on the measurement of some attribute of the product and is determined by a suitable quantitative method. In general, potencies of biotechnological/biological products tested by different laboratories can be compared in a meaningful way only if expressed in relation to that of an appropriate reference material. For that purpose, a reference material calibrated directly or indirectly against the corresponding national or international reference material should be included in the assay.

4.2.2 Potency studies should be performed at appropriate intervals as defined in the stability protocol and the results should be reported in units of biological activity calibrated, whenever possible, against nationally or internationally recognized standard. Where no national or international reference standards exist, the assay results may be reported in in-house derived units using a characterized reference material.

4.2.3 conjugation of the active biological ingredient(s) to a second moiety or binding to an adjuvant. Dissociation of the active biological ingredient(s) from the carrier used in conjugates or adjuvants should be examined in real-time/real- temperature studies (including conditions encountered during shipment). The assessment of the stability of such products may be difficult since, in some cases, in vitro tests for biological activity and physicochemical characterization are impractical or provide inaccurate results. Appropriate strategies (e.g., testing the product prior to conjugation/binding, assessing the release of the active compound from the second moiety, in vivo assays) or the use of an appropriate surrogate test should be considered to overcome the inadequacies of in vitro testing.

4.3. Purity and Molecular Characterization

4.3.1 For the purpose of stability testing of the products described in this guideline, purity is a relative term. Due to the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a biological product is extremely difficult to determine. Thus, the purity of a biological product should be typically assessed by more than one method and the purity value derived is method dependent. For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products.

4.3.2 The degree of purity, as well as individual and total amounts of degradation products of the biological product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies.

4.3.3 The use of relevant physicochemical, biochemical and immunochemical analytical methodologies should permit a comprehensive characterization of the drug substance and/or drug product (e.g., molecular size, charge, hydrophobicity) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation or fragmentation during storage. As examples, methods that may contribute to this include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (e.g., reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography), and peptide

mapping.

4.3.4 Wherever significant qualitative or quantitative changes indicative of degradation product formation is detected during long-term, accelerated and/or stress stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products

4.3.5 Within the long-term stability program. Acceptable limits should be proposed and justified, considering the levels observed in material used in preclinical and clinical studies.

4.3.6 For substances that cannot be properly characterized or products for which an exact analysis of the purity cannot be determined through routine analytical methods, the applicant should propose and justify alternative testing methods.

4.4. Other Product Characteristics

The following product characteristics, though not specifically relating to-/biological products, should be monitored and reported for the final product.

Visual appearance of the product (colour and opacity for solutions/suspensions; colour, texture and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilized cakes, pH, and moisture level of powders and lyophilized products.

Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf-life.

Additives (e.g., Stabilizers, preservatives or excipients may degrade during the dating period of the drug product. If there is any indication during preliminary stability studies that reaction or degradation of such materials adversely affects the quality of the drug product, these items may need to be monitored during the stability program.

The container/closure has the potential to adversely affect the product and should be carefully evaluated (see below).

5. STORAGE CONDITIONS

5.1. Temperature

Since most finished biological products need precisely defined storage temperatures, the storage conditions for the real-time/real-temperature stability studies may be confined to the proposed storage temperature.

5.2. Humidity

5.2.1 Biological products are generally distributed in containers protecting them against humidity. Therefore, where it can be demonstrated that the proposed containers (and conditions of storage) afford sufficient protection against high and low humidity, stability tests at different relative humidities can usually be omitted. Where humidity-protecting containers are not used, appropriate stability data should be provided.

5.3. Accelerated and Stress Conditions

5.3.1 As previously noted, the shelf life should be based on real-time/real-temperature data. However, it is strongly suggested that studies be conducted on the active biological substance and final product under accelerated and stress conditions.

5.3.2 Studies under accelerated conditions may provide useful support data for establishing the shelf life, provide product stability information for future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation, scale-up), assist in validation of analytical methods for the stability program, or generate information which may help elucidate the degradation profile of the active biological substance or final product.

5.3.3 Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also, for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions.

5.4. Container closure system

5.4.1 Changes in the quality of the product may occur due to the interactions between the formulated biological product and the container closure system. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampoules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality.

5.4.2 Data should be s submitted for all different container closure system combinations that will be marketed.

5.4.3 In addition to the standard data necessary for a conventional single-use vial, the applicant should demonstrate that the closure used with a multiple-dose vial is capable of withstanding the conditions of repeated insertions and withdrawals so that the product retains its full potency, purity, and quality for the maximum period specified in the instructions-for-use on containers, carton, and/professional information (in-use stability). Such labelling should be in accordance with SAHPRA requirements.

5.5. Stability after Reconstitution of Freeze-Dried Product

The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, carton, and/or package inserts. Such labelling should be in accordance with SAHPRA requirements.

6. TESTING FREQUENCY

6.1 The shelf-lives of biological products may vary from days to several years. Thus, it is difficult to draft uniform guidelines regarding the stability study duration and testing frequency that would be applicable to all types of biological products. With only a few exceptions, however, the shelf-lives for existing products and potential future products will be within the range of 0.5 to 5 years. Therefore, the guidance is based upon expected shelf-lives in that range. This takes into account the fact that degradation of biological products may not be governed by the same factors during different intervals of a long storage period.

6.2 When shelf-lives of 1 year or less are proposed, the real-time stability studies should be conducted monthly for the first 3 months and at 3-month intervals thereafter.

6.3 For products with proposed shelf-lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter.

6.4 While the testing intervals listed above may be appropriate in the pre-approval or pre-registration stage, reduced testing may be appropriate after approval or registration where data are available that demonstrate adequate stability.

6.5 Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to submit a protocol which supports elimination of specific test intervals (e.g., 9-month testing) for post- approval/post-registration, long-term studies.

7. SPECIFICATIONS

7.1 Recommendations for maximum acceptable losses of activity, limits for physicochemical changes, or degradation during the proposed shelf-life have not been developed for individual types or groups of biological products but will be considered on a case-by-case basis.

7.2 Each product should retain its specifications within established limits for safety, purity, and potency throughout its proposed shelf-life. These specifications and limits should be derived from all available information using the appropriate statistical methods.

7.3 The use of different specifications for release and shelf life should be supported by sufficient data to demonstrate that clinical performance is not affected.

8. LABELLING

8.1 For most /biological active biological substances and final products, precisely defined storage temperatures are recommended. Specific recommendations should be stated, particularly for active biological substances and final products that cannot tolerate freezing. These conditions, and where appropriate, recommendations for protection against light and/or humidity, should appear on containers, cartons, and/or package inserts. Such labelling should be in accordance with SAHPRA requirements.

9. PRESENTATION OF STABILITY DATA

9.1 The criteria for acceptance of each parameter (minimum and maximum values), relating to Stability should be stated.

9.2 The actual analytical results obtained at the commencement (zero time) and at nominated time intervals throughout the trial (for example 0, 3, 6, 9, 12, 18, 24, 30, 36 months, which can if necessary, be adapted to suit the product) should be provided in a tabulated form. For products predicted to degrade rapidly, more frequent sampling is necessary

10.3 The container closure system used should be clearly indicated, e.g. the type, nature, grade and colour of the material of the container and closure should be stated.

10.4 Storage conditions should be clearly defined in respect of the temperature, light, opening and closing of container, whether stored upright or inverted.

10.5 The name and strength of the product, dosage form, lot size, lot number, name of final product manufacturer, manufacturer of active biological ingredient, dates of final product manufacture and initial testing, should be stated.

10.6 All results obtained should be discussed and conclusions drawn from the stability studies' data. A shelf- life should be derived from the results. Explanations should be given where necessary, e.g. for anomalous or unusual results, change in method.

10.7 The stability data should be presented in tabulated format, e.g.:

Product Name: Batch No.: Batch Size: Date of Manufacture: Date of commencement of stability study:					Packaging (material and pack sizes): Storage conditions: Name of manufacturer: Manufacturer of API: Time intervals (months)		
Title of Specification	Limits	0	3	6	9	12	24

11. REFERENCES

11.1 ICH_Q5C Quality of biotechnological products: stability testing of biotechnological/biological products.

11.2 ICH Q1D Bracketing and matrixing designs for stability testing of new drug substances and products.

11.3 WHO Draft guidelines on stability evaluation of vaccines (WHO/BS/06.2049)

12. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision [***2.60_Biological Medicines Stability Guideline _March 2019 _v1***]. It will be reviewed on this timeframe or as and when required