قـرار وزاري رقم (343) لسنة 2025

بشأن الدليل الإرشادي الكويتي لدراسات الثباتية للأدوية البشرية والمواد الفعالة الدوائية

وزيـر الصحة:

- بعد الاطلاع على أحكام المرسـومين بقانون ونظام الخدمة المدنية وتعديلاتهما.
- وعلى أحكام القانون رقم 28 لسـنة 1996 في شـأن تنظيم مهنة الصـيدلة وتداول الأدوية والمعدل بالقانون رقم 30 لسـنة 2016 ولائحتهما التنفيذية.
- وعلى القرار الوزاري رقم (341) لسـنة 2025 بشـأن تسـجيل الأدوية البشرية وتداولها.
- وبناء على مقتضيات مصلحة العمل، وما عرضه علينا السيد/ وكيل الوزارة.

قـرر

مادة أولى

يعتمد الدليل الإرشـادي الكويتي لمتطلبات دراسـات الثباتية للأدوية البشـرية والمواد الفعالة الدوائية المرفق بهذا القرار المتضـمن الشـروط والضوابط اللازمة لتقديم بيانات دراسات الثباتية في ملفات التسجيل وتجديد التسـجيل وطلبات التغييرات على الأدوية المسـجلة التي تتطلب دراسة الثباتية للأدوية البشرية وتحديد شروط التخزين المناسبة للمستحضر الدوائي.

مادة ثانية

يبلغ هذا القرار من يلزم لتنفيذه، ويعمل به اعتباراً من تاريخ صـدوره، وينشر في الجريدة الرسمية.

وزيـر الصحة

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صدر في: 2 رجب 1447هـ

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Kuwait Guideline for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products

الدليل الإرشادي الكويتي لدراسات الثباتية للأدوية البشرية والمواد الفعالة الدوائية

ملحق القرار الوزاري رقم (343) لسنة 2025

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Introduction

Purpose and Scope

This guideline outlines the requirements for the design and submission of stability studies for pharmaceutical products intended for registration in the State of Kuwait. These guidelines are adapted from International Conference on Harmonisation (ICH) on stability guidelines and the World Health Organization (WHO) guidelines on stability testing of active pharmaceutical ingredients and finished pharmaceutical products. The guidance applies to drug substances and drug products for human use, including chemical and biological entities.

Objectives and Applicability

This guideline establishes a unified framework for the design, conduct, and evaluation of stability studies required to support the registration of pharmaceutical products in the State of Kuwait. Its objective is to ensure that products retain their intended quality, safety, and efficacy throughout their shelf life when stored under the climatic conditions representative of Kuwait, which is classified under Climatic Zones III and IV.

The guideline is based on internationally recognized principles outlined in the ICH and WHO guidances and is adapted to address the regulatory and environmental context specific to Kuwait. It provides clarity on the expectations for long-term, accelerated, and in-use stability testing, and outlines acceptable approaches for reduced study designs, such as bracketing and matrixing, where scientifically justified.This guideline applies to all pharmaceutical products intended for registration in Kuwait, including new chemical entities, biologics and generics. It also applies to post-approval submissions involving significant variations, renewals, and re-registrations requiring updated stability data. Furthermore, it is recommended that these requirements be progressively applied to

Active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

Batch. A defined quantity of starting material, packaging material or finished pharmaceutical product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Bracketing. The design of a stability schedule such that only samples at the extremes of certain design factors, e.g. strength and 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. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container-closure system (refer to ICH Q1D).

Climatic zone. The zones into which the world is divided based on the prevailing annual climatic conditions (see reference to the living document "Long-term stability testing conditions as identified by WHO Member products already on the market, with appropriate transitional arrangements made in alignment with regulatory milestones such as renewals.

Guiding Principles and International Harmonization

This guideline is aligned with internationally recognized principles to ensure consistency in the design, conduct, and evaluation of stability studies. It draws primarily from the ICH Q1 series guidelines, with additional reference to ICH Q5C for biotechnological and biological products. Relevant provisions from the World Health Organization (WHO), particularly the Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (WHO TRS No. 1010, Annex 10), have also been incorporated to support harmonization and account for Kuwait's classification under Climatic Zones III and IV.

To facilitate international alignment and ensure consistent product quality, safety, and efficacy throughout shelf life, Medicine and Medical Products Registration and Regulatory Administration is committed to harmonizing its regulatory framework with ICH, WHO, and GCC standards.

This document has been adapted from ICH guidelines to reflect Kuwait's regulatory environment. Certain sections have been modified, reorganized, or excluded to address local requirements and implementation needs.

Definitions and Terminology

Unless otherwise specified, terms used in this guideline align with those defined in the ICH & WHO stability guidelines.

Accelerated testing. Studies designed to increase the rate of chemical degradation and physical change of an active pharmaceutical ingredient or finished pharmaceutical product by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longerterm chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

variations to multisource products.

Expiry date. The date given on the individual container (usually on the label) of a product up to and including which the active pharmaceutical ingredient and finished pharmaceutical product are expected to remain within specifications if stored under the long-term conditions at which stability was established. It is set for each batch by adding the shelf life to the date of manufacture.

Finished pharmaceutical product. A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

Gulf Health Council (GHC) – The Gulf Health Council (GHC) is a specialized health organization established under the umbrella of the Gulf Cooperation Council (GCC). It operates as a regional regulatory and coordination body for health-related initiatives among member states, which include Saudi Arabia, Kuwait, the United Arab Emirates, Qatar, Bahrain, and Oman.

Impermeable containers. Containers that provide a permanent barrier to the passage of gases or solvents, e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms (refer to 2.2.7.2).

Impurity – Any component of the drug substance (bulk material) or drug product (final container product) which is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product.

In-use period. A period of time during which a reconstituted preparation of the finished dosage form in a multidose container, or a moisture-sensitive product in a large-format final container (e.g. high-density polyethylene (HDPE) bottles of 500) can be used after opening.

Intermediate – For biotechnological/ biological products, a material produced during a manufacturing process which is not the drug substance or the drug product but whose manufacture is critical to the successful

production of the drug substance or the drug 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 of time prior to further processing.

Long-term stability studies. Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an active pharmaceutical ingredient or finished pharmaceutical product, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the retest period or the shelf life, to confirm the projected retest period and shelf life, and to recommend storage conditions.

Manufacturing Scale Production – Manufacture at the scale typically encountered in a facility intended for product production for marketing.

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 finished pharmaceutical 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 (refer to ICH Q1D).

Ministry of Health (MOH) – Kuwait: The Ministry of Health is the central governmental authority responsible for regulating, planning, and overseeing healthcare services in the State of Kuwait.

New active pharmaceutical ingredient. Active pharmaceutical ingredient that has not been previously authorized as a medicine for use in humans in the country in question.

Ongoing stability study. The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf life) of the active pharmaceutical ingredient, or confirm or extend the shelf life of the finished pharmaceutical product.

Pilot-Plant Scale – The production of the drug substance or drug 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.

Pilot-scale batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

Primary batch. A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, as the case may be. Primary batch requirements are outlined in 2.1.3 and 2.2.3 for the API and FPP, respectively.

Production batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application. provisional shelf life. A provisional expiry date that is based on acceptable accelerated and available long-term data for the finished pharmaceutical product to be marketed in the proposed container-closure system.

Release specification. The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an active pharmaceutical ingredient or finished

States" 1).

Commitment batches. Production batches of an active pharmaceutical ingredient or finished pharmaceutical product for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Conjugated Product – A conjugated product is made up of an active ingredient (for example, peptide, carbohydrate) bound covalently or noncovalently to a carrier (for example, protein, peptide, inorganic mineral) with the objective of improving the efficacy or stability of the product.

Container-Closure System. The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the finished pharmaceutical product. A packaging system is equivalent to a container-closure system.

Degradation Product – A molecule resulting from a change in the drug 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 biotechnological/ biological products some degradation products may be active.

Dosage form. The form of the finished pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

Excipient. A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a finished pharmaceutical product.

Existing active pharmaceutical ingredient. An active pharmaceutical ingredient that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by the World Health Organization, but requires the filing of a dossier. This would include, for example, new product dossiers and

that an active pharmaceutical ingredient or finished pharmaceutical product should meet throughout its retest period or shelf life.

Significant change. (See sections 1.1.7 and 1.2.7.) "Significant change" for an active pharmaceutical ingredient (API) is defined as failure to meet its specification. In general "significant change" for a finished pharmaceutical product is defined as: a 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures.

Any degradation product exceeding its acceptance criterion.

• Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

• failure to meet the acceptance criterion for pH; or

• failure to meet the acceptance criteria for dissolution for 12 dosage units.

specification. A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which an active pharmaceutical ingredient or finished pharmaceutical product should conform to be considered acceptable for its intended use. See Release specification and Shelf-life specification.

stability-indicating methods. Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the active pharmaceutical ingredient (API) or finished pharmaceutical product, and that are specific so that the content of the API, degradation products and other components of interest can be accurately measured without interference.

stress testing (of the active pharmaceutical ingredient (API)). Studies undertaken to elucidate the intrinsic stability of an API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

stress testing (of the finished pharmaceutical product (FPP)). Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photostability testing and specific testing on certain products (e.g. metered-dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting stability data. Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf life and storage conditions.

utilization period. See in-use period.

Variations. A change to any aspect of a pharmaceutical product, including but not limited to, the change of use of a starting material, a change to formulation, method or site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

Section 1: Adapted from ICH Q1F

1.1 Active pharmaceutical ingredient

1.1.1 General

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be studied during stability testing of an API are listed in the examples of testing parameters (Annex 1). The selection of potential attributes and time points to be tested should be justified.

The retest period or shelf life assigned to the API by the API manufacturer should be derived from stability testing data.

Manufacturer should state clearly the retest period or expiry of their APIs, and to include a commitment to submit the long term data covering the same, if the one at the time of submission cover only the minimum requirement i.e. 12 months. Retest period should not exceed 5 years from the date of manufacture of the API.

1.1.2 Stress testing

Stress testing of the API can help identify the likely degradation products, which in turn can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

For an API the following approaches may be used:

• when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;

• when no published data are available, stress testing should be performed.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperature (in 10 °C increments (for example, at 50 °C, 60 °C) above the temperature used for accelerated testing), humidity (for example, 75% relative humidity (RH) or greater) and, where appropriate, oxidation and photolysis of the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension.

Assessing the necessity for photostability testing should be an integral part of a stress testing strategy. More details can be found in ICH Q1B.

The objective of stress testing is to identify primary degradation products and not to completely degrade the API. The conditions studied should cause degradation to occur to a small extent, typically 10–30% loss of API as determined by assay when compared with non-degraded API. The target should be chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days the API is considered stable under the particular stress condition. However, in this case the stress conditions employed should be justified.

Although examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures, it may not be necessary to examine specifically for

months), from a six month study is recommended. Where it is expected (based on development experience) that results from accelerated studies are likely to approach significant change criteria, additional testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

1.1.7 Storage conditions

In general, an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage condition tolerances are defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

For new APIs, the long-term testing should normally have taken place over a minimum of 12 months for the number of batches specified in section 1.1.3 at the time of submission, and should be continued for a period of time sufficient to cover the proposed retest period or shelf life. Data from the accelerated storage condition, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term and accelerated storage conditions for APIs are detailed in sections 1.1.7.1–1.1.7.3. The general case applies if the API is not specifically covered by a subsequent section.

certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions. Results from these studies will form an integral part of the information provided to regulatory authorities.

1.1.3 Selection of batches

Data from stability studies on at least three primary batches of the API should normally be provided. The batches should be manufactured at a minimum of pilot scale by the same synthesis route as production batches, and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The overall quality of the batches of API placed on stability studies should be representative of the quality of the material to be made on a production scale.

1.1.4 Container–closure system

The stability studies should be conducted on the API packaged in a container closure system that is the same as, or simulates, the packaging proposed for storage and distribution.

1.1.5 Specification

Stability studies should include testing of stability-indicating attributes of the API, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes. A guide to the potential attributes to be tested in the stability studies is provided in Annex 1.

Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies.

1.1.6 Testing frequency

For long-term studies, the frequency of testing should be sufficient to establish the stability profile of the API.

For APIs with a proposed retest period or shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed retest period or shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6

shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.

1.1.7.3 Active pharmaceutical ingredients intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	−20 °C ± 5 °C	12 months

In the rare case of any API of nonbiological origin being intended for storage in a freezer, the retest period or shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

1.1.7.4 Active pharmaceutical ingredients intended for storage below −20 °C

APIs intended for storage below −20 °C should be treated on a case-by-case basis.

1.1.8 Stability commitments

When the available long-term stability data on primary batches do not cover the proposed retest period or shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the retest period or shelf life.

Where the submission includes long-term stability data on three production batches covering the proposed retest period or shelf life, a post approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

– if the submission includes data from stability studies on three production batches, a commitment should be made to continue these studies through the proposed retest period or shelf life;

Alternative storage conditions can be used if justified.

1.1.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

Note: Medicine and Medical Products Registration and Regulatory Administration will accept long-term stability data generated at 25 °C ± 2 °C/60 % RH ± 5 % RH for any API or finished product that cannot withstand 30 °C, provided the dossier contains a robust scientific justification (e.g., degradation-pathway analysis, literature or prior market experience), six-month accelerated data at 40 °C/75 % RH showing no significant change as defined in Section 1.1.7, evidence that the proposed commercial primary pack offers moisture- and oxygen-barrier properties at least equal to those used during testing, and an outer-carton label bearing the statement "Do not store above 25 °C."

1.1.7.2 Active pharmaceutical ingredients intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated	30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

Data on refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed retest period should be based on the data available at the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition a discussion should be provided addressing the effect of short term excursions outside the label storage condition, e.g. during

from several batches, the overall retest period or shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction). Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches, where appropriate, to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the retest period or shelf life can be undertaken if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (please refer to ICH Q1E).

Any evaluation should cover not only the assay but also the levels of degradation products and other stability-indicating attributes.

1.1.10 Statements and labelling

A storage statement should be established for display on the label based on the stability evaluation of the API. Where applicable, specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as "ambient conditions" or "room temperature" should be avoided.

The recommended labelling statements for use when supported by the stability studies are provided in Annex 2.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

After this retest period a batch of API destined

– if the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, up to a total of at least three, in long-term stability studies through the proposed retest period or shelf life;

– if the submission does not include stability data on production batches, a commitment should be made to place the first three production batches (see section 1.1.3) on long-term stability studies through the proposed retest period or shelf life.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified. See also section 1.1.11 Ongoing stability studies.

1.1.9 Evaluation

The purpose of the stability study is to establish – based on testing a minimum of three batches of the API, unless otherwise justified, and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological and microbiological tests) – a retest period or shelf life applicable to all future batches of the API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period or shelf life.

The data may show so little degradation and so little variability that it is apparent from looking at them that the requested retest period or shelf life will be granted. Under these circumstances it is normally unnecessary to go through the statistical analysis with appropriate scientific justification.

One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. P values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data

months in the first year and then annually to confirm the stability.

In certain situations additional batches should be included in the stability programme and may require more frequent testing. For example, a stability study should be initiated after any significant change or significant deviation of the synthetic route, process or container-closure system that may have an impact upon the stability of the API.

Out-of-specification (OOS) results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained and should be available on site. This summary should be subjected to periodic review.

1.2 Finished pharmaceutical product

1.2.1 General

The design of the stability studies for the FPP should be based on knowledge of the behaviour and properties of the API, information from stability studies on the API and on experience gained from preformulation studies, similar marketed formulations and investigational FPPs. The likely changes during storage and the rationale for the selection of attributes to be tested in the stability studies should be stated.

1.2.2 Stress testing

Photostability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. More details can be found in other guidelines (ICH Q1B). Additional stress testing of specific types of dosage forms may be appropriate, e.g. cyclic studies for semi-solid products or freeze-thaw studies for liquid products.

1.2.3 Selection of batches

For FPPs containing new APIs, data from stability studies should be provided on at least three primary batches of each proposed strength of the FPP. Two of the three batches should be at least pilot-scale batches and the third batch can be smaller, if justified (see example below).

for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics) it is more appropriate to establish a shelf life than a retest period.

1.1.11 Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the retest period or shelf life in all future batches.

The ongoing stability programme should be described in a written protocol and the results presented in a formal report that should be available on site.

The protocol for an ongoing stability programme should extend to the end of the retest period or shelf life and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the API labelling, should be used);
- other applicable parameters specific to the API.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and generally should be tested at least every 6

secondary packaging can migrate into the product, the secondary packaging may also form part of the packaging system for stability samples. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

1.2.5 Specification

Stability studies should include testing of stability-indicating attributes of the FPP, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant or antimicrobial preservatives) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed in Annex 1. Analytical procedures should be fully validated and stability-indicating. Whether and to what extent replication should be performed will depend on the results of validation studies. Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during development of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

1.2.6 Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the FPP.

For FPPs containing existing APIs (e.g. generics), data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25,000 or 50,000 tablets or capsules) of each proposed strength of the FPP.

The term "complicated FPP" includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Solid oral products considered "complicated" include modifiedrelease FPPs, products containing problematical APIs such as ritonavir and FDCs containing APIs such as rifampicin or an artemisinin.

The primary batches should be of the same formulation and packaged in the same container-closure system as that proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.

When a batch size smaller than pilot scale is used as a primary batch, data or a discussion is required to confirm that the smaller batch is representative of the intended production size, including its formulation and method of manufacture.

Where possible, batches of the FPP should be manufactured using different batches of the API(s) at least one batch from each supplier.

Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied (refer to ICH Q1D).

1.2.4 Container-closure system

Stability testing should be conducted on the dosage form packaged in the primary container-closure systems proposed for marketing. If the secondary container-closure system has protective properties, and labelling clearly indicates that the product is to be stored in the primary and secondary packaging (e.g. "store tablets in blisters in the provided cartons"), or if the product is packaged in a semi-permeable container where components from the

rationale for the orientation, may need to be included in a protocol where contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids and semisolids), or where there has been a change in the container-closure system.

Storage condition tolerances are usually defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The period of data collection required at the time of submission may be shortened in some circumstances, for example, to address shortages of medicines.

For FPPs containing new APIs, long-term testing should cover a minimum of 12 months at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf-life.

FPPs containing existing APIs (generic products) that are marketed in the country of origin, long term stability study supporting the complete proposed shelf-life should be completed before registration approval.

Additional data accumulated during the assessment period of the registration application should be submitted to the authorities when submitting data in response to outstanding questions. Data from the accelerated storage condition, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term and accelerated conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section. Alternative storage

For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf life (e.g., 0, 3, 6, 9, 12, 18, 24, 36 months).

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, testing should be increased either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated 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.

The initial date of storage should be considered t0 and stability time points should be defined as a date with respect to t0. For example, if t0 is 1 January 2020 then the one-month time point corresponds to either 1 February or 31 January 2020. For each time point, samples should be withdrawn and tested as per the protocol. Testing should be completed as soon as possible. Deviations from the protocol should be recorded and justified.

Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified (refer to ICH Q1D).

1.2.7 Storage conditions

In general an FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.

The orientation of the product during storage, i.e. upright, on the side or inverted, as well as the

potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low RH, as discussed below. Ultimately it should be demonstrated that aqueous based FPPs stored in semi-permeable containers could withstand environments with low RH.

Other comparable approaches can be developed and reported for nonaqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30 °C ± 2 °C/35% RH ± 5% RH	12 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months

- *NMT: not more than

Products meeting the specifications when stored under the accelerated conditions and the long-term storage conditions appropriate to the intended market, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. A significant change in water loss alone at the accelerated storage condition is observed, data should be provided to demonstrate that the pharmaceutical product would not have significant water loss throughout the proposed shelf life if stored at 30 °C/35% 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 an equivalent of three months' storage at 40 °C and 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 an equivalent of three months' storage at 40 °C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studies at the low RH as recommended in the table above (for either long-term or accelerated testing) is to perform the stability studies under higher RH and to derive the water loss at the low RH through calculation. This can be achieved by experimentally determining the permeation coefficient for the container-closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two 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 FPP.

Example of 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 rate of water loss at the low RH is to multiply the rate of water loss measured at an alternative RH at the same temperature, by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative RH over the storage period should be demonstrated.

For example, at a given temperature, e.g. 40 °C, the calculated rate of water loss during storage at NMT 25% RH is the rate of water loss measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Low-Humidity Testing Conditions	Alternative Testing Condition	Ratio of Water Loss Rates	Calculation
30 °C/35% RH	30 °C/65% RH	1.9	(100−35)/(100−65)
30 °C/35% RH	30 °C/75% RH	2.6	(100−35)/(100−75)
40 °C/NMT 25% RH	40 °C/75% RH	3.0	(100−25)/(100−75)

Valid water loss rate ratios at RH conditions other than those shown in the table above can also be used.

1.2.7.4 FPPs intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated	30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

- Whether accelerated stability studies are performed at 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 30 °C/65% RH.

If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss. Data from refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf life should be based on the data available from the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition, a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product throughout six months when a significant change has occurred within the first three months of accelerated studies at the specific condition chosen in accordance with the risk analysis.

1.2.7.5 FPPs intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	−20 °C ± 5 °C	12 months

For FPPs intended for storage in a freezer, the shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

1.2.7.6 FPPs intended for storage below −20 °C

FPPs intended for storage at temperatures below −20 °C should be treated on a case-by-case basis.

1.2.8 Stability commitments

One or more of the following commitments should be made.

– When the available long-term stability data on primary batches do not cover the

conditions can be used if justified.

1.2.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months *
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

Note: Medicine and Medical Products Registration and Regulatory Administration will accept long-term stability data generated at 25 °C ± 2 °C/60 % RH ± 5 % RH for any API or finished product that cannot withstand 30 °C, provided the dossier contains a robust scientific justification (e.g., degradation-pathway analysis, literature or prior market experience), six-month accelerated data at 40 °C/75 % RH showing no significant change as defined in Section 1.1.7, evidence that the proposed commercial primary pack offers moisture- and oxygen-barrier properties at least equal to those used during testing, and an outer-carton label bearing the statement "Do not store above 25 °C."

1.2.7.2 FPPs packaged in impermeable containers

Parameters required to classify the packaging materials as permeable or impermeable depend on the characteristics of the packaging material, such as sealing, thickness and permeability coefficient. The suitability of the packaging material used for a particular product is determined by its product characteristics. Containers generally considered to be moisture-impermeable include glass ampoules.

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus stability studies for products stored in impermeable containers can be conducted under any controlled or ambient RH condition.

1.2.7.3 FPPs packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the statistical analysis. One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. P values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction). Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve. Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken, if justified. This justification should be based on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (refer to ICH Q1E). Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes.

1.2.10 Statements and labelling

proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies postapproval throughout the proposed shelf life. This is the primary batch stability commitment.

– If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to place the next production batches, up to a total of at least three, on long-term stability studies throughout the proposed shelf life and on accelerated studies for six months. This is the production batch stability commitment.

– For each product, an ongoing stability programme is required to monitor the product over its shelf life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. See 1.2.13. This is the ongoing stability commitment.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

1.2.9 Evaluation

The primary stability programme should be described in a written protocol and the results presented in a formal report as outlined in 1.2.13.

A systematic approach should be adopted to the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (e.g. dissolution rate for solid oral dosage forms).

Where appropriate, a summary of additional knowledge and an understanding of stability gained from supporting studies, modelling, predictive tools, etc., may be incorporated to support knowledge gained from the primary stability programme.

The purpose of the stability study is to establish, based on testing a minimum number of batches of the FPP as specified in section 1.2.3, a shelf life and label storage instructions applicable to all future batches of the FPP manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

over the period of the proposed in-use shelf life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semisolids: the content and effectiveness of preservatives need to be studied. A minimum of two batches, at least pilot-scale (with the exceptions outlined in 1.2.3), should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

This testing should be performed on primary batches of the reconstituted or diluted FPP or the solid oral FPP (as above), throughout the proposed in-use period as part of the stability studies at the initial and final time points and, if long-term data covering the shelf life are not available at the time of submission, at 12 months or the last time point at which data will be available. In general this testing need not be repeated on commitment batches (see 1.2.8).Consideration should also be given to hold-time studies of bulk products, e.g. coated tablets prior to final packaging. For example, when the bulk product may be stored for a period exceeding 30 days before being packaged and/or shipped from a manufacturing site to a packaging site, the stability of the bulk product in the intended bulk container should be evaluated and studied. Similar considerations should apply to intermediates that are stored and used for periods exceeding 30 days. Further guidance can be found in the WHO General guidance on hold-time studies.

1.2.12 Variations

Once the FPP has been registered, additional stability studies are required whenever variations are made that may affect the stability of the API or FPP. The applicant should investigate whether or not the intended change will have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability. The scope and design of the stability studies for variations are based on the knowledge and experience acquired on APIs and FPPs.

The available variation guidelines should be consulted for guidance on the expectations regarding stability requirements to support

A storage statement should be established for the label based on the stability evaluation of the FPP. Where applicable, specific instructions should be provided, particularly for FPPs that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided.

There should be a direct link between the storage statement on the label and the demonstrated stability of the FPP. An expiry date should be displayed on the container label.

The labelling statements recommended for use, if supported by the stability studies, are provided in Annex 2. Information on the interpretation and conversion of storage statements for products approved in zone II when the products are to be distributed in zone IV is provided in Annex 3.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see Annex 2).

1.2.11 In-use and hold time stability

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution. Examples include an antibiotic injection supplied as a powder for reconstitution, or a moisture-sensitive or hygroscopic solid oral FPP in a large format multidose container (e.g. high density polyethylene (HDPE) bottle of 500 tablets). In general, a 30-day in-use period is normally considered acceptable without further supporting data.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those that occur in practice, appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature. The physical, chemical and microbial properties of the FPP that are susceptible to change during storage should be determined

shelf-life period and should include, but not be limited to, the following parameters:
- number of batch(es) per strength and different batch sizes, if applicable. The batch size should be recorded, if batch sizes differ;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency (generally at 6 months and annual time points is sufficient for ongoing studies);
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the product labelling, should be used); and other applicable parameters specific to the FPP.

The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example, the frequency of testing as above, or when updating to meet revised recommendations).

The number of batches and frequency of testing should provide sufficient data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol (refer to ICH Q1D).

In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or container closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion. Refer to section 1.2.12 for further details.

OOS results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant competent authorities. The possible impact on batches on changes to the API and FPP. Note that the requirements of the guidelines of the specific regulatory authority or region prevail for a given region; however, in the absence of such guidelines, the WHO Prequalification Team: Medicines guidelines can be applied (10). Depending on the variation, either the results of a stability study or a commitment to conduct such as study is required. Variation guidelines are specific detailed guidelines, therefore the following are general categories and the guidelines should be referred to for the exact circumstances and requirements. In the aforementioned guidance document (10), changes requiring supporting data include certain changes to the API retest period or storage conditions, and to the FPP formulation, manufacturing process, container-closure system, shelf life, in-use period and storage conditions. Other changes, such as certain changes to the API certificate of suitability, certificate of prequalification, manufacturing site or manufacturing process, or certain changes to the FPP manufacturing site, batch size or container-closure system, require a commitment for stability studies to support the variations.

The results of these stability studies should be communicated to the regulatory authorities concerned, following the applicable requirements stipulated in the variation guidelines for the region.

1.2.13 Ongoing stability studies

After a marketing authorization has been granted, the stability of the FPP should be appropriately monitored according to a continuous programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products or dissolution profile) associated with the formulation in the container closure system in which it is marketed. The purpose of the ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label. The ongoing stability programme should be described in a written protocol and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the

program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications. It is understood that during the review and evaluation process, continuing updates of initial stability data may occur.

2.2 Scope

The guidance stated in this annex applies to well-characterised 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-characterised proteins or polypeptides. In addition, the guidance outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the appropriate regulatory authorities. The document does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components.

2.3 Selection of Batches

2.3.1 Drug Substance (Bulk Material)

Where bulk material is to be stored after manufacture but prior to 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. For drug 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 the regulatory agencies with a commitment to place the first 3 manufacturing scale batches into the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

Section 2: Adapted from ICH Q5C

2.1 Introduction

The guidance stated in the ICH harmonised tripartite guideline "Stability Testing of New Drug Substances and Products" (27 October 1993) applies in general to biotechnological/ biological products. However, biotechnological/ biological products do 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. For such products, in which the active components are typically proteins and/or polypeptides, maintenance of molecular conformation and, hence of biological activity, is dependent on noncovalent as well as covalent forces. The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. 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 methodologies. Assays for biological activity, where applicable, 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 biotechnological/ biological product and consider many external conditions which can affect the product's potency, purity and quality. 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

data should occur during the review and evaluation process. The quality of the final container product placed on stability studies should be representative of the quality of the material used in the preclinical and clinical studies. Data from pilot plant scale batches of drug product may be provided at the time the dossier is submitted to the regulatory agencies 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 dating for a product and, in the event that product produced at manufacturing scale does not meet those long-term stability specifications throughout the dating 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.

2.4 Sample Selection

Where one product is distributed in batches differing in fill volume (e.g., 1 millilitre (ml), 2 ml, or 10 ml), unitage (e.g., 10 units, 20 units, or 50 units), or mass (e.g., 1 milligram (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.

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.

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

the long-term stability program after approval. The quality of the batches of drug substance placed into the stability program should be 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 drug 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. The drug 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.

2.3.2 Intermediates

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.

2.3.3 Drug Product (Final Container Product)

Stability information should be provided on at least 3 batches of final container product representative of that which will be used at manufacturing scale. Where possible, batches of final container product included in stability testing should be derived from different batches of bulk material. A minimum of 6 months data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug 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. Product expiration dating will be based upon the actual data submitted in support of the application. Since dating is based upon the realtime/real-temperature data submitted for review, continuing updates of initial stability

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.

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 recognised standard. Where no national or international reference standards exist, the assay results may be reported in in-house derived units using a characterised reference material.

In some biotechnological/ biological products, potency is dependent upon the conjugation of the active ingredient(s) to a second moiety or binding to an adjuvant. Dissociation of the active 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 characterisation 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.

2.8 Purity and Molecular Characterisation

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 biotechnological/ biological product is extremely difficult to determine. Thus, the purity of a biotechnological/ 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.

The degree of purity, as well as individual and total amounts of degradation products of the biotechnological/ biological product entered

assumes that the stability of the intermediate condition samples are 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.

2.4 Stability-Indicating Profile

On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/ biological product. Consequently, the manufacturer should 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 emphasised 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.

2.6 Protocol

The dossier accompanying the application for marketing authorisation should include a detailed protocol for the assessment of the stability of both drug substance and drug product in support of the proposed storage conditions and expiration dating periods. The protocol should include all necessary information which demonstrates the stability of the biotechnological/ biological product throughout the proposed expiration dating period including, for example, well-defined specifications and test intervals. The statistical methods that should be used are described in the tripartite guideline on stability.

2.7 Potency

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

lyophilised 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., stabilisers, 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 affect 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).

2.10 Storage Conditions

2.10.1 Temperature

Since most finished biotechnological/ 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.

2.10.2 Humidity

Biotechnological/ 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.

2.10.3 Accelerated and Stress Conditions

As previously noted, the expiration dating should be based on real-time/real temperature data. However, it is strongly suggested that studies be conducted on the drug substance and drug product under accelerated and stress conditions. Studies under accelerated conditions may provide useful support data for establishing the expiration date, 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 drug substance or 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.

The use of relevant physicochemical, biochemical and immunochemical analytical methodologies should permit a comprehensive characterisation 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. Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated and/or stress stability studies, consideration should be given to potential hazards and to the need for characterisation and quantification of degradation products within the long-term stability program. Acceptable limits should be proposed and justified, taking into account the levels observed in material used in preclinical and clinical studies.

For substances that cannot be properly characterised 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 procedures.

2.9 Other Product Characteristics

The following product characteristics, though not specifically relating to biotechnological/ biological products, should be monitored and reported for the drug product in its final container:

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 lyophilised cakes, pH, and moisture level of powders and

conditions and the maximum storage period specified on containers, packages, and/or package inserts. Such labelling should be in accordance with relevant national/regional requirements.

2.13 Testing Frequency

The shelf-lives of biotechnological/ 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 biotechnological/ 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 biotechnological/ biological products may not be governed by the same factors during different intervals of a long storage period.

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.

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.

While the testing intervals listed above may be appropriate in the pre-approval or pre-licence stage, reduced testing may be appropriate after approval or licensure where data are available that demonstrate adequate stability. 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-licensure, long-term studies.

2.14 Specifications

Although biotechnological/ biological products may be subject to significant losses of activity, physicochemical changes, or degradation during storage, international and national regulations have provided little guidance with respect to distinct release and end of shelf-life specifications. Recommendations for maximum acceptable losses of activity, limits for physicochemical changes, or degradation during drug product. 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. While the tripartite guideline on stability describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological/ biological products. Conditions should be carefully selected on a case-by-case basis.

2.10.4 Light

Applicants should consult the appropriate regulatory authorities on a case-by-case basis to determine guidance for testing.

2.11 Container Closure

Changes in the quality of the product may occur due to the interactions between the formulated biotechnological/ biological product and container/closure. 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. Data should be supplied for all different container/closure combinations that will be marketed.

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, packages, and/or package inserts. Such labelling should be in accordance with relevant national/regional requirements.

2.12 Stability after Reconstitution of Freeze-Dried Product

The stability of freeze-dried products after their reconstitution should be demonstrated for the

and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status.

It is not expected that every test listed be performed at each time point. This can also apply to sterility testing, which may be conducted for most sterile products at least at the beginning and at the end of the stability test period. A validated container-closure integrity test may be used in lieu of sterility testing. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder-filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested at least at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided. Weight loss from plastic containers should be reported over the shelf life.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every test listed be included in the design of a stability protocol for a particular finished pharmaceutical product (FPP) (for example, a test for odour should be performed only when necessary and with due consideration for the analyst's safety).

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol when contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids or

the proposed shelf-life have not been developed for individual types or groups of biotechnological/ biological products but are considered on a case-by-case basis. 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. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that clinical performance is not affected as discussed in the tripartite guideline on stability.

2.15 Labelling

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

Annexes

Annex 1: Examples of testing parameters

Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Since some related substances might only be identified as degradation products in the outcome of the stability studies, all specified related substances should be monitored as part of API stability studies. Other API parameters that may be susceptible to change should also be studied where applicable (e.g. particle size and/or polymorphism when relevant for low-solubility APIs).

Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile

elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and the container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

Nasal sprays: solutions and suspensions

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump.

Topical, ophthalmic and otic preparations

Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, eye drops and cutaneous sprays.

• Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).

• Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.

• Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

Suppositories

Disintegration and dissolution (at 37 °C) and as appropriate for the type, net filled content, rupture time, melting and solidification, semisolids), or where there has been a change in the container closure system.

Tablets

Dissolution, disintegration, water content and hardness/friability. Dispersible tablets should additionally be tested for disintegration (with a limit of not more than 3 minutes) and fineness of dispersion.

Capsules

hard gelatin capsules: brittleness, dissolution, disintegration, water content and level of microbial contamination;

soft gelatin capsules: dissolution, disintegration, level of microbial contamination, pH, leakage and pellicle formation.

Oral solutions, suspensions and emulsions

Formation of precipitate, clarity (for solutions), pH, viscosity, extractables, level of microbial contamination.

Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.

Additionally for emulsions, phase separation, mean size and distribution of dispersed globules should be evaluated.

Powders and granules for oral solution or suspension

Water content and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described above under "Oral solutions suspensions and emulsions" after preparation according to the recommended labelling, through the maximum intended use period.

Metered-dose inhalers and nasal aerosols

Some parameters listed may be assessed during development and not be required subsequently in stability studies. Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractables/leachables from plastic and

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) are listed in Table A10.1.

Table A10.1: Recommended labelling statements for active pharmaceutical ingredients

Testing condition under which the stability of the API has been demonstrated	Recommended labelling statement
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"[b]
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
−20 °C ± 5 °C	"Store in freezer"

- During storage, shipment and distribution of the API, the current Good trade and distribution practices (GTDP) for pharmaceutical starting materials are to be observed.
- Details on storage and labelling requirements can be found in WHO guide to good storage practices for pharmaceuticals .
- [b]"Protect from moisture" should be added as applicable.

Finished pharmaceutical products

The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table A10.2.

Table A10.2: Recommended labelling statements for finished pharmaceutical products

Testing condition under which the stability of the FPP has been demonstrated	Recommended labelling statements[a]
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"[b]
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"

liquefaction/softening time, leakage, pellicles and pH.

Small volume parenterals (SVPs)

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended on the label, should include clarity, colour, pH, sterility, pyrogen/ endotoxin and particulate matter. It may be appropriate to consider monitoring of sterility after reconstitution into a product, e.g. dual-chamber syringe, where it is claimed that reconstitution can be performed without compromising sterility.

• The stability studies for suspension for injection should include, in addition, particle size distribution, dispersibility, specific gravity, resuspendability, rheological properties and dissolution (when applicable). Content uniformity may be considered a stabilityindicating parameter for the primary stability studies of a depot injection such as depomedroxyprogesterone acetate (DMPA) (refer to the WHO Prequalification Team-medicines (PQTm) DMPA guidance document published on the PQTm website: who.int/prequal/).[2]

• The stability studies for emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

Large volume parenteral (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

Transdermal patches

In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

Annex 2: Recommended labelling statements

Active pharmaceutical ingredients

subjected to low temperatures, e.g. liquids and semisolids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

Annex 3: Interpretation of storage statements for products approved in climatic zone II when the products are to be distributed in zone IV

In order to ensure the safe use of medicines in recipient countries, the wording on labelling storage statements must be considered in the context of both the region in and for which the stability studies were conducted and the region(s) in which the products are intended to be distributed. Typical examples of the storage statements for products approved in zone II, with examples of the stability data on which the statements are based and the corresponding WHO-recommended storage statement for distribution in zone IV are provided in Table A10.4.

Table A10.4: Examples of stability data and storage statements for products approved in climatic zone II and WHO-recommended storage statements (for zone IV)

Storage statement for products approved in zone II	Examples of stability data on which the statements are based	WHO-recommended storage statement for products to be distributed in zone IVa
This medicinal product does not require any special storage conditions (EU)	Zone II + Zone IVb + accelerated (FPP is stable at long-term conditions (zones II and IVb), with no significant change at accelerated conditions)	"Do not store above 30 °C"
Do not store above 30 °C (EU)	Zone IVa + accelerated (FPP is stable at longterm conditions, with significant change	"Do not store above 30 °C. Protect from

		−20 °C ± 5 °C	"Store in freezer"

- During storage, shipment and distribution of the FPP, the current good distribution practices (GDP) for pharmaceutical products are to be observed. Details on storage and labelling requirements can be found in WHO guide to good storage practices for pharmaceuticals .
- [b] "Protect from moisture" should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table A10.3.

Table A10.3: Additional labelling statements for use where the result of the stability testing demonstrates limiting factors

Limiting factors	Additional labelling statement, where relevant
Finished pharmaceutical products (FPPs) that cannot tolerate refrigeration	"Do not refrigerate or freeze"[a]
FPPs that cannot tolerate freezing	"Do not freeze"[a]
Light-sensitive FPPs	"Protect from light"
FPPs that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic FPPs	"Store in dry condition"
Packaging (with the packaging format specified in the statement, e.g. bottle, blister)	"Store in the original package" "Keep the container in the outer carton" "Keep the container tightly closed in order to protect from light and moisture"

[a] Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if

at accelerated moisture" conditions)

Note: Zone II is 25 °C/60% RH, zone IVa is 30 °C/65% RH and zone IVb is 30 °C/75% RH.

Note: IVa may be acceptable in lieu of IVb when humidity is not an issue, for example, for storage in glass containers (see 1.2.7.2 of the main text of the Annex).

Annex 4: References

1. ICH. Q1A (R2): Stability Testing of New Drug Substances and Products. Geneva; 2003. database.ich.org

2. ICH. Q1B: Photostability Testing of New Dru g Substances and Products. Geneva; 1996. database.ich.org

3. ICH. Q1C: Stability Testing for New Dosage Forms. Geneva; 1996. database.ich.org

4. ICH Q1F : Stability data package for registration in climatic zones III and IV

5. ICH. Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances an d Products. Geneva; 2002. database.ich.org

6. ICH. Q1E: Evaluation for Stability Data. Geneva; 2004. database.ich.org

7. ICH. Q5C: Stability Testing of Biotechnologi cal/Biological Products.

8. World Health Organization (WHO). Stability Testing of Active Pharmaceuti cal Ingredients and Finished Pharmaceutical Pro ducts. Annex 10, WHO Technical Report Series No. 1010. Geneva; 2018. World Health Organization

9. Executive Board of the Health Ministers' Council for GCC States. GCC Guidelines on Stability Testing of P harmaceutical Products.; 2003