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Saudi Food & Drug Authority

Stability Testing of New Veterinary Drug Substances "Active Pharmaceutical Ingredients (APIs)" and Medicinal Products "Finished Pharmaceutical Products (FPPs)"

Pharmaceutical Products only

Adopted from Veterinary International Conference on Harmonization (VICH) and edited by SFDA

Version 1.0

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Drug Sector

For Comments *Drug.Comments@sfda.gov.sa*

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

Version	Adopted by	Date	Comments
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1. INTRODUCTION

The guideline is adapted from a revised version of the GL3 VICH.

1.1. Objectives of the Guidance

It seeks to illustrate the core stability data package for new veterinary drug substances and medicinal products, then leaves sufficient flexibility to cover the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

1.2. Scope of the Guidance

The guideline addresses the information to be submitted in registration applications for new veterinary drug substances and associated medicinal products. This guidance does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, or clinical trial applications.

Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guidance.

Additional guidance on biotechnological/biological products, new dosage forms and on medicated premixes can be found in VICH guidelines GL17, GL4, and GL8, respectively. Stability testing following first use of the product (e.g., first broaching of a vial) is not covered within this guidance.

1.3. General Principles

The purpose of stability testing is to provide evidence on how the quality of a drug substance or medicinal product varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light, and to establish a re-test period for the drug substance or a shelf life for the medicinal product and recommended storage conditions.

The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the regions of kingdom of Saudi Arabia and the Gulf countries. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guidance addresses climatic zones III and IVa. The principle has been established that stability information generated in the kingdom of Saudi Arabia or the Gulf countries would be mutually acceptable to the other region, provided the information is consistent with this guidance and the labeling is in accord with national/regional requirements.

2. GUIDELINE

2.1. Drug Substance (API)

2.1.1 General

Information on the stability of the drug substance, Active Pharmaceutical Ingredient (API), is an integral part of the systematic approach to stability evaluation.

2.1.2 Stress Testing

Stress testing of the drug substance can help identify the likely degradation products, which can in turn 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 drug substance and the type of medicinal product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. It should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in VICH GL5.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be important to examine specifically for 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.

2.1.3 **Selection of Batches**

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

Other supporting data should be provided.

2.1.4 **Container Closure System**

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

2.1.5 **Specification**

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, is addressed in VICH GL39 and GL40. In addition, specification for degradation products in a drug substance is discussed in GL10 (R).

Stability studies should include testing of those attributes of the drug substance 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. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed should depend on the results from validation studies.

2.1.6 **Testing Frequency**

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period.

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 6-month study is recommended. Where an expectation (based on development experience) exists that the results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or 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, 12 months), from a 12-month study is recommended.

2.1.7 **Storage Conditions**

In general, a drug substance (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, shipment and subsequent use.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities, if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition should be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case should apply if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions may be used, if justified.

2.1.7.1. General case

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a

minimum of 6 months' data from a 12-month study at the intermediate storage condition.

"Significant change" for a drug substance is defined as failure to meet its specification.

2.1.7.2. Drug substances 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	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

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

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g., during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

2.1.7.3. Drug substances 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 Drug substances (API) of non-biological origin being intended for storage in a freezer, the re-test period should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°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.

2.1.7.4. Drug substances intended for storage below -20°C

Drug substances (API) intended for storage below -20°C should be treated on a case-by-case basis.

2.1.8 **Stability Commitment**

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

Where the submission includes long term stability data on three production batches covering the proposed re-test period, 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 at least three production batches, a commitment should be made to continue these studies through the proposed re-test period.
- 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 re-test period and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed re-test period.
- If the submission does not include stability data on production batches, a commitment

should be made to place the first three production batches on long-term stability studies through the proposed re-test period.

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.

2.1.9 **Evaluation**

The purpose of the stability study is to establish, based on testing a minimum of three batches specified in section 2.1.3, unless otherwise justified and authorized, of the drug substance (API) and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a re-test period applicable to all future batches of the drug substance 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 re-test period.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing 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 re-test period 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 consider 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 real-time data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken at approval time, if justified. This justification should be based, for example, 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, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of evaluation linked to medicinal product (FPP) stability and degradation "behavior" during the testing.

2.1.10 **Statements/Labeling**

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided.

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

2.1.11 **Ongoing stability studies**

The stability of the drug substance (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 re-test period in all future batches.

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

The protocol for an ongoing stability programme should extend to the end of the re-test period and 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 methods;
- acceptance criteria;
- 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 labeling, should be used); and
- 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 tested at least annually to confirm the stability. 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 synthetic route, process or container closure system which may have an impact upon the stability of the API.

Out-of-specification results or significant atypical trends should be investigated. Any

confirmed significant change, out-of-specification result, or significant atypical trend 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. This summary should be subjected to periodic review.

2.1. Medicinal Product (FPP)

2.2.1. General

The design of the formal stability studies for the medicinal product, Finished Pharmaceutical Product (FPP), should be based on knowledge of the behavior and properties of the drug substance (API) and from stability studies on the drug substance (API) and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2.2.2. Photostability Testing

Photostability testing should be conducted on at least one primary batch of the medicinal product, if appropriate. The standard conditions for photostability testing are described in VICH GL5.

2.2.3. Selection of Batches

Data from stability studies should be provided on at least three primary batches of the medicinal product. The primary batches should be of the same formulation and packaged in the same container closure system as 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. Two of the three batches should be at least pilot scale batches, and the third one can be smaller, if justified. Where possible, batches of the medicinal product

should be manufactured by using different batches of the drug substance (API).

Stability studies should be performed on each individual strength and container size of the medicinal product unless bracketing or matrixing is applied.

If the product is registered and marketed in the country of origin, at least one of the batches used in submitted stability study should be of a production scale.

For FPP with different API suppliers, stability batches of the FPP should be manufactured using API from the different suppliers (at least one batch from each supplier).

Other supporting data can be provided.

2.2.4. Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). In some cases, a smaller container closure system simulating the actual container closure system for marketing may be acceptable. In these instances, a justification for using a smaller container closure system should be provided. Any available studies carried out on the medicinal product outside its immediate container or in other packaging materials may form a useful part of the stress testing of the dosage form or may be considered as supporting information, respectively.

2.2.5. Specification

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in VICH GL39 and GL40. In addition, specification for degradation products in a medicinal product is addressed in GL11(R).

Stability studies should include testing of those attributes of the medicinal product 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, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). 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 data demonstrating preservative effectiveness of a development batch of the proposed formulation artificially prepared to contain the lowest permitted levels of the antimicrobial preservative(s) according to the shelf-life specification. A single primary stability batch of the medicinal product should be tested for antimicrobial preservative effectiveness (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.

2.2.6. Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the medicinal product (FPP). 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 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed 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 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted 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, 12 months), from a 12-month study is recommended.

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.

2.2.7. Storage Conditions

In general, a medicinal product (FPP) should be evaluated under storage conditions (with appropriate 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.

Stability testing of the medicinal product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long-term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, repeating this testing on commitment batches is not recommended.

The long-term testing should cover a minimum of 6 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities, if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition may be used to evaluate the effect of short-term excursions

outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for medicinal products are detailed in the sections below. The general case should apply if the medicinal product is not specifically covered by a subsequent section. Alternative storage conditions may be used, if justified.

2.2.7.1. General case

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

**For generic products that are marketed in the country of origin, long-term stability study supporting the complete proposed shelf-life should be submitted.*

2.2.7.2. Medicinal products 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 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 medicinal products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers may be conducted under any controlled or ambient humidity condition.

2.2.7.3. Medicinal products packaged in semi-permeable containers

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

Other comparable approaches may be developed and reported for non-aqueous, solvent-based medicinal products.

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long-term	30°C ± 2°C/35% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/ NMT* 25% RH	6 months

*NMT: not more than.

Products meeting either of the long-term storage conditions and the accelerated conditions, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. When 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 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 relative humidity as recommended in the table above (for either long-term or accelerated testing) is to perform the stability studies under higher relative humidity and deriving the water loss at the low relative humidity 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 medicinal products (FPP).

Example of an approach for determining water loss:

For a medicinal product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

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

Low-humidity testing conditions	**Alternative testing condition**	**Ratio of water loss rates**	**Calculation**
25 °C/40% RH	25 °C/60% RH	1.5	(100-40)/(100-60)
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)

*NMT: not more than.

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

2.2.7.4. Medicinal products (FPPs) intended for storage in a refrigerator

Study	**Storage condition**	**Minimum time period covered**

		by data at submission
Long-term	5°C ± 3°C	6 months
Accelerated	30°C ± 2°C/ 65% RH ± 5% RH	6 months

If the medicinal product 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 this guidance, 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 to address 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.

2.2.7.5. Medicinal products (FPPs) intended for storage in a freezer

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long-term	-20°C ± 5°C	6 months

For medicinal products (FPPs) intended for storage in a freezer, the shelf life should be

based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for medicinal products 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.

2.2.7.6. Medicinal products intended for storage below -20°C

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

2.2.8. Stability Commitment

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

Where the submission includes long-term stability data from three production batches as specified in section 2.2.3 covering the proposed shelf life, a post-approval commitment is not recommended. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches specified in section 2.2.3, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.
- If the submission includes data from stability studies on fewer than three production batches specified in section 2.2.3, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.
- If the submission does not include stability data on production batches specified in section 2.2.3, a commitment should be made to place the first three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6

months.

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

2.2.9. Evaluation

A systematic approach should be adopted in 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). The stability data should include the raw analytical data with supportive chromatograms for the tests carried out at the last time point.

The purpose of the stability study is to establish, based on testing a minimum number of batches of the medicinal product (FPPs) as specified in section 2.2.3, a shelf life and label storage instructions applicable to all future batches of the medicinal product (FPPs) 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.

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 unnecessary to go through the formal statistical analysis; it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of 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 may 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 may be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship may be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the shelf life may be undertaken at approval time, if justified. This justification should be based, for example, 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, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

2.2.10. Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the medicinal product (FPP). Where applicable, specific instruction should be provided, particularly for medicinal products (FPP) that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the medicinal product (FPP). An expiration date must be displayed on the

container label.

2.2.11. In-use stability testing

The purpose of in-use stability testing is to establish - where applicable - a period of time during which a multi-dose product can be used whilst retaining quality within an accepted specification once the container is opened.

The registration for a multi-dose product should include either the in-use stability data on which the in-use shelf-life is based or a justification why no in-use shelf-life is established. This justification can also be based on experimental results.

The in-use shelf-life and in-use storage recommendations -if applicable- should be included in the summary of product characteristics (SPC), patient information leaflet (PIL) and on the product's labeling.

a. Selection of batches

A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies (with a commitment to submit the results at the end of shelf-life as soon as they become available).

The batch number, date of manufacture and size of each batch should be stated. The container and closure of the product and, if present, the medicinal device should be equivalent to that proposed for marketing.

If the product is to be supplied in more than one container size or in different strengths, the in-use stability should be applied to the product which presents the greatest susceptibility to change. The choice of the tested product should always be justified.

b. Test design

As far as possible, the test should be designed to simulate the use of the product in practice taking into consideration the filling volume of the container and any dilution/reconstitution before use. At intervals comparable to those which occur in practice appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature. Sampling should take place under normal environmental conditions of use.

The appropriate physical, chemical and microbial properties of the product susceptible to change during storage should be determined 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 remaining amount of the product in the container.

c. Test storage conditions

The product should be stored under the conditions as recommended in the product literature (SPC and PIL) throughout the in-use stability test period.

Any other storage conditions should be justified.

d. Test parameters

The appropriate physical, chemical and microbial properties of the product susceptible to change during use should be monitored. The tests used must be appropriate to individual dosage forms.

The following are examples of test parameters which may need to be studied:

- **Physical:** Color, clarity, closure integrity, particulate matter, particle size.
- **Chemical:** Active substance assay(s), antimicrobial preservative and antioxidant content(s), degradation product level(s), pH.
- **Microbial:** Total viable count, sterility.

e. Analytical procedures

The analytical procedures used in the study should be described and fully validated. Stability indicating assays should be employed.

f. Presentation of the results

The results should be summarized and tabulated. If relevant, the results should be presented graphically.

g. Evaluation

Conclusions based on the data provided should be stated and any anomalous results should be explained.

Where applicable and justified an in-use shelf-life specification should be given.
In-use stability data should be used to determine whether or not a declaration of an in-use shelf-life and storage conditions are necessary.

2.2.12. Variations

Once the medicinal product (FPP) has been registered, additional stability studies are required whenever variations that may affect the stability of the API or FPP are made.
The following are examples of such changes:

- change in the manufacturing process;
- change in the composition of the medicinal product (FPP);
- change of the immediate packaging;
- change in the manufacturing process of an API.
- Extension of shelf life.

In all cases of variations, the applicant should investigate whether the intended change will or will not 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 and changes are based on the knowledge and experience acquired on APIs and FPPs.

The results of these stability studies should be communicated to the regulatory authorities concerned.

2.2.13. Ongoing stability studies

After a marketing authorization has been granted, the stability of the medicinal product (FPP) should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities 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.

This mainly applies to the medicinal product (FPP) in the container closure system in which it is supplied, but consideration should also be given to inclusion in the programme of bulk products. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied. Generally, this would form part of development studies, but where this need has not been foreseen, inclusion of a one-off study in the ongoing stability programme could provide the necessary data. Similar considerations could apply to intermediates that are stored and used over prolonged periods.

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 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 different batch sizes are employed;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- 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 product labeling, should be used);
- 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, or when updating to meet revised recommendations). Testing frequency may be at 6-months interval for the confirmation of the provisional shelf life, or every 12 months for well established products.

Ongoing stability submitted to support product re-registration or variations should be carried out on batches manufactured within the last five years from the application date. 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.

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.

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to the relevant competent authorities. The possible impact on batches on 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.

3. Glossary

The definitions given below apply to the terms used in this guideline and provided to facilitate interpretation of the guidelines.

Accelerated testing:

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or medicinal product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, should be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Active pharmaceutical ingredient (API) (also referred to as "drug substance or Active pharmaceutical ingredient (API)" in this guidance):

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

Climatic zones:

The four zones in the world that are distinguished by their characteristic based on the prevailing annual climatic conditions.

Five climatic zones can be distinguished for the purpose of worldwide stability testing.

Climatic Zone	**Definition**
I	Temperate climate
II	Subtropical and Mediterranean climate
III *	Hot/dry climate

IV a *	Hot/humid climate
IV b	Hot/very humid climate

* GCC States are categorized in climatic zones III & IV a.

Commitment batches:

Production batches of a drug substance or medicinal product for which the stability studies are initiated or completed postapproval through a commitment made in the registration application.

Container closure system:

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the medicinal product. A packaging system is equivalent to a container closure system.

Dosage form:

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Excipient:

A substance or compound, other than the API and packaging materials, that is intended or designated to be used in the manufacture of a FPP. In other words; Anything other than the drug substance in the dosage form.

Expiration date:

The date given on the individual container (usually on the label) of a product up to and including which the API and FPP are expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture. If stored under defined conditions and after which it should not be used.

Finished pharmaceutical product (FPP) (also referred to as "medicinal product or Finished pharmaceutical product (FPP)" in this guidance):

A product that has undergone all stages of production, including packaging in its final

container and labeling. An FPP may contain one or more APIs.

Formal stability studies:

Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a medicinal product.

Impermeable containers:

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Long-term testing:

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an API or FPP, 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 re-test period or the shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions.

Mass balance:

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

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 medicinal product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature:

A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or medicinal product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and considers the Arrhenius equation. When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes *(J. Pharm. Sci.*, 60:927-929, 1971) may be used.

New Veterinary Drug Substance (also referred to as "drug substance or Active pharmaceutical ingredient (API)" in this guidance):

The designated therapeutic moiety that has not been previously registered in a region or member state for use in a veterinary medicinal product (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved substance.

New Veterinary Medicinal Product (also referred to as "medicinal product or Finished pharmaceutical product (FPP)" in this guidance):

A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., containing a new or existing drug substance which has not previously been registered in a region or member state, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

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 re-test period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

Pilot scale batch:

A batch of a drug substance (API) or medicinal product (FPP) manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. 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 a drug substance (API) or medicinal product (FPP) used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance (API) should be at least a pilot scale batch. For a medicinal product (FPP), two of the three batches should be at least pilot scale batch, and the third batch may be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch:

A batch of a drug substance (API) or medicinal product (FPP) manufactured at production scale by using production equipment in a production facility as specified in the application.

Provisional shelf-life:

A provisional expiry date which is based on acceptable accelerated and available long-term data for the FPP 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 API or FPP at the time of its release.

Re-test date:

The date after which samples of the drug substance (API) should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given medicinal product.

Re-test period:

The period of time during which the drug substance (API) is expected to remain within its specification and, therefore, may be used in the manufacture of a given medicinal

product (FPP), provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance (API) destined for use in the manufacture of a medicinal product (FPP) should be re-tested for compliance with the specification and then used immediately. A batch of drug substance (API) may be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

Semi-permeable containers:

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Significant change

In general, "significant change" for an FPP 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. (*Note*: other values may be applied, if justified, to certain products, such as multivitamins and herbal preparations.)
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. color, 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.

Shelf life (also referred to as expiration dating period):

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

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 API or FPP should conform to be considered acceptable for its intended use.

Specification - Release:

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a medicinal product at the time of its release.

Specification - Shelf life:

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a medicinal product should meet throughout its shelf life.

Stability indicating methods:

Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the API or FPP, and that are specific so that the content of the API, degradation products, and other components of interest can be accurately measured without interference.

Stability studies (stability testing:)

Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period (or shelf-life) of an API or the shelf-life of an FPP.

Storage condition tolerances:

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

Stress testing (drug substance):

Studies undertaken to elucidate the intrinsic stability of the drug substance. 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 (medicinal product (FPP)):

Studies undertaken to assess the effect of severe conditions on the medicinal product. Such studies include photostability testing (see VICH GL5) and specific testing of certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data:

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include:

1. stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing;
2. information regarding test results on containers;
3. other scientific rationales.

4. References

- *VICH GL58 stability testing of new veterinary drug substances and medicinal products in climatic zones III and IV*
- *VICH GL4 Stability Testing of New Veterinary Dosage Forms*
- *VICH GL5 Photostability Testing of New Veterinary Drug Substances and Medicinal Products*
- *VICH GL8 Stability Testing for Medicated Premixes*
- *VICH GL10(R) Impurities in New Veterinary Drug Substances*
- *VICH GL11(R) Impurities in New Veterinary Medicinal Products*
- *VICH GL17 Stability Testing of Biotechnological/Biological Veterinary Medicinal Products*
- *VICH GL39 Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances*
- *VICH GL40 Specifications: Test Procedures and Acceptance Criteria for New Biotechnological/Biological Veterinary Medicinal Products.*

Appendix 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). Other API parameters that may be susceptible to change should also be studied where applicable.

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 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 applies in particular to sterility testing, which may be conducted for most sterile products at the beginning and at the end of the stability test period. 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.