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(REVIEW ARTICLE)

ICH guidelines – "Q" series (quality guidelines) - A review

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Abstract

ICH- international council for harmonization of technical requirements for pharmaceuticals for human use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH mission is to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed and registered in the most resource –efficient manner. Harmonization achievements in quality area include pivotal milestone such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more manufacturing practice (GMP) risk management.

Keywords: ICH guidelines; Q- series; Harmonization; Stability studies; GMP

Q1A Stability testing of new drugs substances and products

Approvals given by the steering committee of the second revision directly under step 4 without further public constitution to include consequences of the adoption of Q1F (stability data package for registration applications in climatic zone 3&4) and recruitment for adoption to the 3 ICH regulatory bodies. The following guideline is a revised version of the ICH Q1A guideline and defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. It does not seek necessarily to cover the testing for registration in or export to other areas of the world.

The guideline seeks to exemplify the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass 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. The guideline addresses the submitted in registration applications for new information to be molecular entities and associated drug products. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc.

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

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidelines Q1C and Q5C, respectively. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

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The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States. 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 guideline addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the EC, Japan and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guideline and the labeling is in accord with national/regional requirements [1].

Guidelines

Drug substances

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

Includes

- Stress testing.
- Selection of batches
- Container closure system
- Specification
- Testing frequency
- Storage condition
- Stability commitment
- Evaluation
- Statements / labeling

Drug product

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance 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.

Includes

- Photo stability testing.
- Selection of batches.
- Container closure system.
- Specification.
- Testing frequency.
- Storage conditions.
- Stability commitment.
- Evaluation.
- Statements/ labeling.

The purpose of this is to outline the changes made in Q1A(R) that result from adoption of ICH Q1F “Stability Data Package for Registration Applications in Climatic Zones III and IV”.

These changes are:

1. The intermediate storage condition has been changed from 30 °C±2 °C/60% RH±5% RH to 30 °C±2 °C/65% RH±5% RH in the following sections:
    - Drug Substance - Storage Conditions - General Case
    - Drug Product - Storage Conditions - General Case
    - Drug products packaged in semi-permeable containers
2. 30 °C±2 °C/65% RH±5% RH can be a suitable alternative long-term storage condition to 25 °C±2 °C/60% RH±5% in the following sections:
    - Drug Substance - Storage Conditions - General Case

- Drug Product - Storage Conditions - General Case

3. 30 °C±2 °C/35% RH±5% RH has been added as a suitable alternative long-term storage condition to 25 °C±2 °C/40% RH±5% and the corresponding example for the ratio of water-loss rates has been included in the following section:
   - Drug products packaged in semi-permeable containers
4. Mid-stream switch of the intermediate storage condition from 30 °C±2 °C/60% RH±5% RH to 30 °C±2 °C/65% RH±5% RH can be appropriate provided that the respective storage conditions and the date of the switch are clearly documented and stated in the registration application.

It is recommended that registration applications contain data from complete studies at the intermediate storage condition 30 °C±2 °C/65% RH±5% RH, if applicable, by three years after the date of publication of this revised guideline in the respective ICH tripartite region.

Q1B Stability testing

Photo stability testing of new drug substances and products

The ICH harmonized tripartite guideline covering the stability testing of new drug substances and Products (hereafter referred to as the Parent Guideline) notes that light testing should be an integral part of stress testing. This document is an annex to the Parent Guideline and addresses the recommendations for photo stability testing.

Drug substances and drug product

- Presentation of samples
- Analysis of samples
- Judgment of results

Immediate (primary) pack is that constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

Marketing pack is the combination of immediate pack and other secondary packaging such as a carton.

Forced degradation testing studies are those undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substances, are used to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.

Confirmatory studies are those undertaken to establish photo stability characteristics under standardized conditions. These studies are used to identify precautionary measures needed in manufacturing or formulation and whether light resistant packaging and/or special labeling is needed to mitigate exposure to light. For the confirmatory studies, the batches should be selected according to batch selection for long-term and accelerated testing which is described in the Parent Guideline [2].

Q1C Stability testing for new dosage form

The ICH harmonized tripartite guideline on stability testing of new drug substances and products was issued on October 27, 1993. This document is an annex to the ICH parent stability guideline and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.

New dosage form

A new dosage form is defined as a drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority.

Such pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems. (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension).

Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (eg. 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases [3].

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

This guideline is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH Q1A(R) Harmonized Tripartite guideline on Stability Testing of New Drug Substances and Products (hereafter referred to as the parent guideline).

This document provides guidance on bracketing and matrixing study designs. Specific principles are defined in this guideline for situations in which bracketing or matrixing can be applied.

A full study design is one in which samples for every combination of all design factors are tested at all times points. A reduced design is one in which samples for every factor combination is not all tested at all times point. A reduced design can be a suitable alternative to a full design when multiple design factors are involved. Any reduced design should have the ability to adequately predict the retest period or shelf life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter retest period or shelf life than could be derived from a full design due to the reduced amount of data collected.

Bracketing

As defined in the glossary to the parent guideline, bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all times point as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

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

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations. Examples include but are not limited to capsules of different strengths made with different fill plug sizes from the same powder blend, tablets of different strengths manufactured by compressing varying amounts of the same granulation, and oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants, flavorings).

With justification, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation. Such justification can include a demonstration of comparable stability profiles among the different strengths of clinical or development batches.

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

Matrixing

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

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems.

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

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

tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants or flavorings).

Other examples of design factors that can be matrixes include batches made by using the same process and equipment, and container sizes and/or fills in the same container closure system.

With justification, matrixing designs can be applied, for example, to different strengths where the relative amounts of drug substance and excipients change or where different excipients are used or to different container closure systems. Justification should generally be based on supporting data. For example, to matrix across two different closures or container closure systems, supporting data could be supplied showing relative moisture vapor transmission rates or similar protection against light. Alternatively, supporting data could be supplied to show that the drug product is not affected by oxygen, moisture, or light [4].

Q1E Evaluation of stability data

This guideline is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline "Q1A(R) Stability Testing of New Drug Substances and Products" (hereafter referred to as the parent guideline) to propose a retest period or shelf life in a registration application. This guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by "available data from the stability study under the long-term storage condition" (hereafter referred to as long-term data). The guidance on the evaluation and statistical analysis of stability data provided in the parent guideline is brief in nature and limited in scope. The parent guideline states that regression analysis is an appropriate approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for batch pool ability be performed using a level of significance of 0.25. However, the parent guideline includes few details and does not cover situations where multiple factors are involved in a full- or reduced-design study.

This guideline is an expansion of the guidance presented in the Evaluation sections of the parent guideline.

This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. The guideline provides recommendations on establishing retest periods and shelf lives for drug substances and drug products intended for storage at or below "room temperature"*. It covers stability studies using single- or multi-factor designs and full or reduced designs.

*Note: The term "room temperature" refers to the general customary environment and should not be inferred to be the storage statement for labeling.

ICH Q6A and Q6B should be consulted for recommendations on the setting and justification of acceptance criteria and ICH Q1D should be referenced for recommendations on the use of full- versus reduced-design studies.

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life [5].

Q2 (R1) Validation of analytical procedures

Text and methodology

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the EC, Japan and USA. This document does not necessarily seek to cover the testing that may be required for registration in, or export to, other areas of the world. Furthermore, this text presentation serves as a collection of terms, and their definitions, and is not intended to provide direction on how to accomplish validation. These terms and definitions are meant to bridge the differences that often exist between various compendia and regulators of the EC, Japan and USA.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

Types of analytical procedures to be validated

- The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures: Identification tests;
- Quantitative tests for impurities' content;
- Limit tests for the control of impurities;
- Quantitative tests of the active moiety in Samples of drug substance or drug product or other selected component(s) in the drug product.

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures are equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behaviour, chemical reactivity, etc) to that of a reference standard;
- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test;
- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

- Accuracy
- Precision
- Repeatability
- Intermediate Precision
- Specificity
- Detection Limit
- Quantization Limit
- Linearity
- Range

Each of these validation characteristics is defined in the attached Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- Changes in the synthesis of the drug substance;

- Changes in the composition of the finished product;
- Changes in the analytical procedure.

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well [6].

Q3A (R2) Impurities in new drug substances

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin.

Impurities in new drug substances are addressed from two perspectives:

Chemistry aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures; and

Safety aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

Classification of impurities

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Guideline Q3C on Residual Solvents).

Excluded from this document are: (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as Good Manufacturing Practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

Reporting impurity content of batches

Analytical results should be provided in the application for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. Quantitative results should be presented numerically, and not in general terms such as "complies", "meets limit" etc. Any impurity at a level greater than (>) the reporting threshold (see Attachment 1) and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. Below 1.0%, the results should be reported to two decimal places (e.g., 0.06%, 0.13%); at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%). Results should be rounded using conventional rules (see Attachment 2). Tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, e.g., retention time. If a higher reporting threshold is proposed, it should be fully justified. All impurities at a level greater than (>) the reporting threshold should be summed and reported as total impurities.

When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of representative batches from analytical validation studies showing separation and detect ability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The applicant should ensure that complete impurity profiles (e.g., chromatograms) of individual batches are available, if requested.

Tabulation should be provided that links the specific new drug substance batch to each safety study and each clinical study in which the new drug substance has been used.

For each batch of the new drug substance, the report should include:

- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Impurity content, individual and total
- Use of batches
- Reference to analytical procedure used

Listing of impurities in specification

In summary, the new drug substance specification should include, where applicable, the following list of impurities:

- Organic impurities
- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
- Total impurities [7].

Q3B (R2) Impurities in new drug products

This document provides guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state.

This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as "degradation products" in this guideline). Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products.

Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline. This guideline also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guideline:

biological/biotechnological products, peptide, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin. Also excluded from this document are: (1) extraneous contaminants that should not occur in new drug products and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

The applicant should summarize the degradation products observed during manufacture and/or stability studies of the new drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition, the applicant should summarize any laboratory studies conducted to detect degradation products in the new drug product. This summary should also include test results of batches manufactured during the development process and batches representative of the proposed commercial process. A rationale should be provided for exclusion of those impurities that are not degradation products (e.g., process impurities from the drug substance and impurities arising from excipients). The impurity profiles of the batches representative of the proposed commercial process should be compared with the profiles of batches used in development and any differences discussed.

Any degradation product observed in stability studies conducted at the recommended storage condition should be identified when present at a level greater than (>) the identification thresholds given in Attachment 1. When identification of a degradation product is not feasible, a summary of the laboratory studies demonstrating the unsuccessful efforts to identify it should be included in the registration application.

Degradation products present at a level of not more than (≤) the identification threshold generally would not need to be identified. However, analytical procedures should be developed for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacological effects at levels not more than (≤) the identification threshold. In unusual circumstances, technical factors (e.g., manufacturing capability, a low drug substance to excipient ratio, or the use of excipients that are crude products of animal or plant origin) can be considered as part of the justification for selection of alternative thresholds based upon manufacturing experience with the proposed commercial process.

For each batch of the new drug product described in the registration application, the documentation should include:

- Batch identity, strength, and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Immediate container closure
- Degradation product content, individual and total
- Use of batch (e.g., clinical studies, stability studies)
- Reference to analytical procedure used
- Batch number of the drug substance used in the new drug product
- Storage conditions for stability studies

In summary, the new drug product specification should include, where applicable, the following list of degradation products:

- Each specified identified degradation product
- Each specified unidentified degradation product
- Any unspecified degradation product with an acceptance criterion of not more than (≤) the identification threshold
- Total degradation products [8].

Q3C (R5) Residual solvents

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (*Class 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (*Class 2*) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (*Class 3)* should be used where practical.

The lists are not exhaustive and other solvents can be used and later added to the lists. Recommended limits of Class 1 and 2 solvents or classification of solvents may change as new safety data becomes available. Supporting safety data in a marketing application for a new drug product containing a new solvent may be based on concepts in this guideline or the concept of qualification of impurities as expressed in the guideline for drug substance (Q3A, *Impurities in New Drug Substances*) or drug product (Q3B, *Impurities in New Drug Products*), or all three guidelines.

Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug product. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that recommended in this guideline, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. Drug product should also be tested if a solvent is used during its manufacture.

This guideline does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guideline applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short term (30 days or less) or topical application. Justification for these levels should be made on a case by case basis.

Classification of residual solvents by risk assessment

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance.

Residual solvents they were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1 solvents: Solvents to be avoided

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 solvents: Solvents to be limited

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

Class 3 solvents: Solvents with low toxic potential

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day [9].

Q3D Guidelines for elemental impurities

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. There are three parts of this guideline: the evaluation of the toxicity data for potential elemental impurities; the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern; and application of a risk-based approach to control elemental impurities in drug products. An applicant is not expected to tighten the limits based on process capability, provided that the elemental impurities in drug products do not exceed the PDEs. The PDEs established in this guideline are considered to be protective of public health for all patient populations. In some cases, lower levels of elemental impurities may be warranted when levels below toxicity thresholds have been shown to have an impact on other quality attributes of the drug product (e.g., element catalyzed degradation of drug substances). In addition, for elements with high PDEs, other limits may have to be considered from a pharmaceutical quality perspective and other guidelines should be consulted (e.g., ICH Q3A).

This guideline presents a process to assess and control elemental impurities in the drug product using the principles of risk management as described in ICH Q9. This process provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product.

The guideline applies to new finished drug products (as defined in ICH Q6A and Q6B) and new drug products containing existing drug substances. The drug products containing purified proteins and polypeptides (including proteins and polypeptides produced from recombinant or non-recombinant origins), their derivatives, and products of which they are components (e.g., conjugates) are within the scope of this guideline, as are drug products containing synthetically produced polypeptides, polynucleotide, and oligosaccharides.

This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives, dialyses solutions not intended for systemic circulation, and elements that are intentionally included in the drug product for therapeutic benefit. This guideline does not apply to products based on genes (gene therapy), cells (cell therapy) and tissue (tissue engineering). In some regions, these products are known as advanced therapy medicinal products.

This guideline does not apply to drug products used during clinical research stages of development. As the commercial process is developed, the principles contained in this guideline can be useful in evaluating elemental impurities that may be present in a new drug product.

Application of Q3D to existing products is not expected prior to 36 months after publication of the guideline by ICH.

The factors considered in the safety assessment for establishing the PDE are listed below in approximate order of relevance:

- The likely oxidation state of the element in the drug product;
- Human exposure and safety data when it provided applicable information;
- The most relevant animal study;
- Route of administration;
- The relevant endpoint(s).

Elements classification

- Class:1
- Class:2
- Class :2A

- Class:2B
- Class: 3 [10].

Q4B Evaluation and recommendation of pharmacopeia texts for use in "ICH" regions

This document describes a process for the evaluation and recommendation by the Q4B Expert Working Group (EWG) of selected pharmacopoeia texts to facilitate their recognition by regulatory authorities for use as interchangeable in the ICH regions [11].

Q5A (R1) Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin

This document is concerned with testing and evaluation of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin (i.e., mammalian, avian, insect) and outlines data that should be submitted in the marketing application/registration package. For the purposes of this document the term virus excludes nonconventional transmissible agents like those associated with Bovine Spongiform Encephalopathy (BSE) and scrape. Applicants are encouraged to discuss issues associated with BSE with the regulatory authorities.

The scope of the document covers products derived from cell cultures initiated from characterized cell banks. It covers products derived from *in vitro* cell culture, such as interferon's, monoclonal antibodies and recombinant DNA-derived products including recombinant subunit vaccines, and also includes products derived from hybridoma cells grown *in vivo* as ascites. In this latter case, special considerations apply and additional information on testing cells propagated *in vivo* is contained in Appendix 1. Inactivated vaccines, all live vaccines containing self-replicating agents, and genetically engineered live vectors are excluded from the scope of this document.

The risk of viral contamination is a feature common to all biotechnology products derived from cell lines. Such contamination could have serious clinical consequences and can arise from the contamination of the source cell lines themselves (cell substrates) or from adventitious introduction of virus during production. To date, however, biotechnology products derived from cell lines have not been implicated in the transmission of viruses. Nevertheless, it is expected that the safety of these products with regard to viral contamination can be reasonably assured only by the application of a virus testing program and assessment of virus removal and inactivation achieved by the manufacturing process, as outlined below.

Three principal, complementary approaches have evolved to control the potential viral contamination of biotechnology products:

- Selecting and testing cell lines and other raw materials, including media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans;
- Assessing the capacity of the production processes to clear infectious viruses;
- Testing the product at appropriate steps of production for absence of contaminating infectious viruses.

All testing suffers from the inherent limitation of quantitative virus assays, i.e., that the ability to detect low viral concentrations depends for statistical reasons on the size of the sample. Therefore, no single approach will necessarily establish the safety of a product. Confidence that infectious virus is absent from the final product will in many instances not be derived solely from direct testing for their presence, but also from a demonstration that the purification regimen is capable of removing and/or inactivating the viruses.

The type and extent of viral tests and viral clearance studies required at different steps of production will depend on various factors and should be considered on a case-by-case and step-by-step basis. The factors that should be taken into account include the extent of cell bank characterization and qualification, the nature of any viruses detected, culture medium constituents, culture methods, facility and equipment design, the results of viral tests after cell culture, the ability of the process to clear viruses, and the type of product and its intended clinical use.

The purpose of this document is to provide a general framework for virus testing, experiments for the assessment of viral clearance and a recommended approach for the design of viral tests and viral clearance studies. Related information is described in the appendices and selected definitions are provided in the glossary.

The manufacturers should adjust the recommendations presented here to their specific product and its production process. The approach used by manufacturers in their overall strategy for ensuring viral safety should be explained and justified. In addition to the detailed data which is provided, an overall summary of the viral safety assessment would be useful in facilitating the review by regulatory authorities. This summary should contain a brief description of all aspects of the viral safety studies and strategies used to prevent virus contamination as they pertain to this document [12].

Q5B Quality of biotechnological products

This document presents guidance regarding the characterization of the expression construct for the production of recombinant DNA protein products in eukaryotic and prokaryotic cells. This document is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant DNA derived proteins. This document is not intended to cover the whole quality aspect of rDNA derived medicinal products.

The expression construct is defined as the expression vector containing the coding sequence of the recombinant protein. Segments of the expression construct should be analyzed using nucleic acid techniques in conjunction with other tests performed on the purified recombinant protein for assuring the quality and consistency of the final product. Analysis of the expression construct at the nucleic acid level should be considered as part of the overall evaluation of quality, taking into account that this testing only evaluates neither the coding sequence of a recombinant gene and not the translational fidelity nor other characteristics of the recombinant protein, such as secondary structure, tertiary structure, and post-translational modifications [13].

Q5C Quality of biotechnological products

Stability testing of biotechnological/biological products

The guidance stated in this annex applies to well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors and tumor necrosis factors), erythropoietin's, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulin, monoclonal antibodies, and vaccines consisting of well-characterized 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 [14].

Q5D Derivation and characterization of cell substrates

This guideline covers cell substrates having a cell banking system. In this document, "cell substrate" refers to microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the desired biotechnological/biological products for human *in vivo* or *ex vivo* use. Reagents for *in vitro* diagnostic use are outside the scope of this document. Animal sources of cell lines include all those of metazoan origin. Both continuous cell lines of indefinite *in vitro* lifespan and diploid cells of finite *in vitro* lifespan are included. Microbial sources include bacteria, fungi, yeast, and other unicellular life forms.

"Biotechnological/biological products" refers to any products prepared from cells cultivated from cell banks with the exception of microbial metabolites such as, for example, antibiotics, amino acids, carbohydrates, and other low molecular weight substances. Cell banks used to prepare gene therapy products or vaccines should follow the recommendations presented in this document. Some biological products, such as certain viral vaccines, are prepared in primary cell cultures derived directly from animal tissues or organs. Primary cells are not banked and therefore are not addressed by this document.

It is important to provide supportive documentation which describes the history of the cell substrate that is used in the manufacture of a biotechnological/biological product, as well as any parental cell line from which it was totally or partially derived. Events during the research and development phases of the cell substrate may contribute significantly to assessment of the risks associated with the use of that particular cell substrate for production. The information supplied in this regard is meant to facilitate an overall evaluation which will ensure the quality and safety of the product.

Careful records of the manipulation of the cell substrate should be maintained throughout its development. Description of cell history is only one tool of many used for cell substrate characterization. In general, deficiencies in documented history may not, by itself, be an impediment to product approval, but extensive deficiencies will result in increased reliance on other methods to characterize the cell substrate [15].

Q5E Comparability of biotechnological/biological products subject to changes in their manufacturing process

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guideline is intended to assist in the collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical or clinical strategy. The main emphasis of the document is on quality aspects [16].

Q6A Specifications: test procedures and acceptance criteria, for new drug substances and new drug products

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan.

The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, and process validation, and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, i.e., those tests, procedures, and acceptance criteria which play a major role in assuring the quality of the new drug substance and new drug product at release and during shelf life. Specifications are an important component of quality assurance, but are not it only

Component. All of the considerations listed above are necessary to ensure consistent production of drug substances and drug products of high quality.

This guideline addresses only the marketing approval of new drug products (including combination products) and, where applicable, new drug substances; it does not address drug substances or drug products during the clinical research stages of drug development. This guideline may be applicable to synthetic and semi-synthetic antibiotics and synthetic peptides of low molecular weight; however, it is not sufficient to adequately describe specifications of higher molecular weight peptides and polypeptides, and biotechnological/biological products. The ICH Guideline Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products address guideline specifications, tests and procedures for biotechnological/biological products. Radiopharmaceuticals, products of fermentation, oligonucleotides, herbal products and crude products of animal or plant origin are similarly not covered.

Guidance is provided with regard to acceptance criteria which should be established for all new drug substances and new drug products, i.e. universal acceptance criteria, and those that are considered specific to individual drug substances and/or dosage forms. This guideline should not be considered all encompassing. New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when justified.

Dosage forms addressed in this guideline include solid oral dosage forms, liquid oral dosage forms, and parenterals (small and large volume). This is not meant to be an all-inclusive list, or to limit the number of dosage forms to which this guideline applies. The dosage forms presented serve as models, which may be applicable to other dosage forms which have not been discussed. The extended application of the concepts in this guideline to other dosage forms, e.g., to inhalation dosage forms (powders, solutions, etc.), to topical formulations (creams, ointments, gels), and to transdermal systems, is encouraged [17].

Q6B Specifications: Test procedures and acceptance criteria for biotechnological/biological products

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

This document does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components. A separate ICH Guideline, "Specifications: Test Procedures and Acceptance Criteria for New Drugs Substances and New Drug Products: Chemical Substances" addresses specifications, and other criteria for chemical substances.

This document does not recommend specific test procedures or specific acceptance criteria nor does it apply to the regulation of preclinical and/or clinical research material [18].

Q7 Good manufacturing practice guide for active pharmaceutical ingredients

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this Guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and the related controls. In this Guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this Guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, or aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This Guide is not intended to define registration/filing requirements or modify pharmacopoeia requirements. This Guide does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met [19].

Q8 (R2) Pharmaceutical development

This guideline is intended to provide guidance on the contents of section 3.2.P.2 (pharmaceutical development) for drug products as defined in the scope of module 3 of the common technical document (ich guideline m4). The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline to a particular type of product, applicants can consult with the appropriate regulatory authorities [20].

Q9 Quality risk management

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labelling materials in drug (medicinal) products, biological and biotechnological products).

Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk [21].

Q10 Pharmaceutical quality system

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among, and the different goals of each stage.

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

Pharmaceutical development

- Drug substance development;
- Formulation development;
- Manufacture of investigational products;
- Delivery system development;
- Manufacturing process development and scale-up;
- Analytical method development.

Technology transfer

- New product transfers during Development through Manufacturing;
- Transfers within or between manufacturing and testing sites for marketed products.

Commercial manufacturing

- Acquisition and control of materials;
- Provision of facilities, utilities, and equipment;
- Production (including packaging and labeling);
- Quality control and assurance;
- Release;
- Storage;
- Distribution (excluding wholesaler activities).

Product discontinuation

- Retention of documentation;
- Sample retention;
- Continued product assessment and reporting [22].

Q11 Development and manufacture of drug substances (chemical entities and biotechnological/biological entities)

It addresses aspects of development and manufacture that pertain to drug substance, including the presence of steps designed to reduce impurities. In addition, ICH Q11 provides further clarification on the principles and concepts described in ICH Guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) as they pertain to the development and manufacture of drug substance.

A company can choose to follow different approaches in developing a drug substance. For the purpose of this guideline, the terms "traditional" and "enhanced" are used to differentiate two possible approaches. In a traditional approach, set points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and develop appropriate control strategies applicable over the lifecycle of the drug substance which may include the establishment of design space(s). As discussed in ICH Q8 for drug product, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provided in the application for marketing authorisation.

Traditional and enhanced approaches are not mutually exclusive. A company can use either a traditional approach or an enhanced approach to drug substance development, or a combination of both.

This guideline is applicable to drug substances as defined in the Scope sections of ICH Guidelines Q6A and Q6B, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. The guideline does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages. Regional requirements for post-approval changes are not covered by this guideline [23].

Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management

This guideline provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. Effective implementation of the tools and enablers described in this guideline should enhance industry's ability to manage many CMC changes effectively under the firm's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation [24].

Q13 Continuous manufacturing of drug substances and drug products

The new ICH guideline will establish harmonized scientific and technical requirements needed to fulfill regulatory expectations for the implementation and assessment of CM to improve access to medicines. An ICH guideline would facilitate international harmonization and could reduce barriers to the adoption of CM technology [25].

Q14 Analytical procedure development

The new guideline is proposed to harmonize the scientific approaches of Analytical Procedure Development, and to provide the principles relating to the description of Analytical Procedure Development process. This new guideline is intended to improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures [26].

Conclusion

Harmonization achievements in the quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Compliance with ethical standards

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There is no conflict of interest among authors.

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