INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8

Current *Step 4* version
dated 10 November 2005

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q8
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Current *Step 4* version

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ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 10 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

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1. INTRODUCTION

1.1 Objective of the Guideline

This guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format.

The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management (for definition, see ICH Q9) to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle* of a product. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.

1.2 Scope

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.

2. PHARMACEUTICAL DEVELOPMENT

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space*, specifications, and manufacturing controls.

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality* cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is

* See Glossary for definition

considered to be a change and would normally initiate a regulatory post approval change process.

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. Summary tables and graphs are encouraged where they add clarity and facilitate review.

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified. Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

In addition, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters. Inclusion of this additional information in this section provides an opportunity to demonstrate a higher degree of understanding of material attributes, manufacturing processes and their controls. This scientific understanding facilitates establishment of an expanded design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- risk-based regulatory decisions (reviews and inspections);
- manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
- reduction of post-approval submissions;
- real-time quality control, leading to a reduction of end-product release testing.

To realise this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters. This understanding can be gained by application of, for example, formal experimental designs*, process analytical technology (PAT)*, and/or prior knowledge. Appropriate use of quality risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge.

The design and conduct of pharmaceutical development studies should be consistent with their intended scientific purpose. It should be recognized that the level of knowledge gained, and not the volume of data, provides the basis for science-based submissions and their regulatory evaluation.

2.1 Components of the Drug Product

2.1.1 Drug Substance

The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were

* See Glossary for definition

specifically designed into the drug substance (e.g., solid state properties), should be identified and discussed. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These properties could be inter-related and might need to be considered in combination.

To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted. For example, the ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* describes some of the circumstances in which drug product studies are recommended (e.g., Decision Tree #3 and #4 (Part 2)). This approach applies equally for the ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*. The knowledge gained from the studies investigating the potential effect of drug substance properties on drug product performance can be used, as appropriate, to justify elements of the drug substance specification (3.2.S.4.5).

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated.

2.1.2 Excipients

The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. This should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not (e.g., processing aids). Compatibility of excipients with other excipients, where relevant (for example, combination of preservatives in a dual preservative system), should be established. The ability of excipients (e.g., antioxidants, penetration enhancers, disintegrants, release controlling agents) to provide their intended functionality, and to perform throughout the intended drug product shelf life, should also be demonstrated. The information on excipient performance can be used, as appropriate, to justify the choice and quality attributes of the excipient, and to support the justification of the drug product specification (3.2.P.5.6).

Information to support the safety of excipients, when appropriate, should be cross-referenced (3.2.P.4.6).

2.2 Drug Product

2.2.1 Formulation Development

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration. Information from formal experimental designs can be useful in identifying critical or interacting variables that might be important to ensure the quality of the drug product.

The summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components (e.g., the properties of the drug substance,

excipients, container closure system, any relevant dosing device), the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug product(s).

Any excipient ranges included in the batch formula (3.2.P.3.2) should be justified in this section of the application; this justification can often be based on the experience gained during development or manufacture.

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Information from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) that links clinical formulations to the proposed commercial formulation described in 3.2.P.1 should be summarized and a cross-reference to the studies (with study numbers) should be provided. Where attempts have been made to establish an in vitro/in vivo correlation, the results of those studies, and a cross-reference to the studies (with study numbers), should be provided in this section. A successful correlation can assist in the selection of appropriate dissolution acceptance criteria, and can potentially reduce the need for further bioequivalence studies following changes to the product or its manufacturing process.

Any special design features of the drug product (e.g., tablet score line, overfill, anti-counterfeiting measure as it affects the drug product) should be identified and a rationale provided for their use.

2.2.2 Overages

In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.

Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product. Information should be provided on the 1) amount of overage, 2) reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and 3) justification for the amount of overage. The overage should be included in the amount of drug substance listed in the batch formula (3.2.P.3.2).

2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties relevant to the safety, performance or manufacturability of the drug product should be identified and discussed. This includes the physiological implications of drug substance and formulation attributes. Studies could include, for example, the development of a test for respirable fraction of an inhaled product. Similarly, information supporting the selection of dissolution vs. disintegration testing, or other means to assure drug release, and the development and suitability of the chosen test, could be provided in this section. See also ICH *Q6A Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances*; Decision Tree #4 (Part 3) and Decision Tree #7 (Part 1) or ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*. The discussion should cross-reference any relevant stability data in 3.2.P.8.3.

2.3 Manufacturing Process Development

The selection, the control, and any improvement of the manufacturing process described in 3.2.P.3.3 (i.e., intended for commercial production batches) should be explained. It is important to consider the critical formulation attributes, together with the available manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of the components. Appropriateness of the equipment used for the intended products should be discussed. Process development studies should provide the basis for process improvement, process validation, continuous process verification* (where applicable), and any process control requirements. Where appropriate, such studies should address microbiological as well as physical and chemical attributes. The knowledge gained from process development studies can be used, as appropriate, to justify the drug product specification (3.2.P.5.6).

The manufacturing process development programme or process improvement programme should identify any critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality.

For those products intended to be sterile an appropriate method of sterilization for the drug product and primary packaging material should be chosen and the choice justified.

Significant differences between the manufacturing processes used to produce batches for pivotal clinical trials (safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the process described in 3.2.P.3.3 should be discussed. The discussion should summarise the influence of the differences on the performance, manufacturability and quality of the product. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (3.2.P.5.4). The information should include, for example, (1) the identity (e.g., batch number) and use of the batches produced (e.g., bioequivalence study batch number), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).

In order to provide flexibility for future process improvement, when describing the development of the manufacturing process, it is useful to describe measurement systems that allow monitoring of critical attributes or process end-points. Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding. The process control strategies that provide process adjustment capabilities to ensure control of all critical attributes should be described.

An assessment of the ability of the process to reliably produce a product of the intended quality (e.g., the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment) can be provided. An understanding of process robustness* can be useful in risk assessment and risk reduction (see ICH *Q9 Quality Risk Management* glossary for definition) and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools (see ICH *Q9 Quality Risk Management*).

* See Glossary for definition

2.4 Container Closure System

The choice and rationale for selection of the container closure system for the commercial product (described in 3.2.P.7) should be discussed. Consideration should be given to the intended use of the drug product and the suitability of the container closure system for storage and transportation (shipping), including the storage and shipping container for bulk drug product, where appropriate.

The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure. A possible interaction between product and container or label should be considered.

The choice of primary packaging materials should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), and safety of materials of construction. Justification for secondary packaging materials should be included, when relevant.

If a dosing device is used (e.g., dropper pipette, pen injection device, dry powder inhaler), it is important to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions which, as far as possible, simulate the use of the product.

2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the drug product should be discussed in this section (3.2.P.2.5). The discussion should include, for example:

- The rationale for performing or not performing microbial limits testing for non sterile drug products (e.g., Decision Tree #8 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products)*;
- The selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial;
- For sterile products, the integrity of the container closure system as it relates to preventing microbial contamination.

Although chemical testing for preservative content is the attribute normally included in the drug product specification, antimicrobial preservative effectiveness should be demonstrated during development. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling micro-organisms by using an antimicrobial preservative effectiveness test. The concentration used should be justified in terms of efficacy and safety, such that the minimum concentration of preservative that gives the required level of efficacy throughout the intended shelf life of the product is used. Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented in this section.

2.6 Compatibility

The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for

the labelling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Similarly, admixture or dilution of products prior to administration (e.g., product added to large volume infusion containers) might need to be addressed.

3. GLOSSARY

Continuous Process Verification:

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Formal Experimental Design:

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as "Design of Experiments".

Lifecycle:

All phases in the life of a product from the initial development through marketing until the product's discontinuation.

Process Analytical Technology (PAT):

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Process Robustness:

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Quality:

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).