European Medicines Agency

May 2000
CPMP/ICH/367/96

**ICH Topic Q 6 A**
**Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances**

**Step 5**

# NOTE FOR GUIDANCE SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

(CPMP/ICH/367/96)

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| TRANSMISSION TO CPMP | September 1997 |
| TRANSMISSION TO INTERESTED PARTIES | September 1997 |
| DEADLINE FOR COMMENTS | March 1998 |
| FINAL APPROVAL BY CPMP | November 1999 |
| DATE FOR COMING INTO OPERATION | May 2000 |

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK

# SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

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# 1. INTRODUCTION

## 1.1 Objective of the guideline

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.

## 1.2 Background

A specification is defined as 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 a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to Good Manufacturing Practices; e.g., suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

## 1.3 Scope of the guideline

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 its 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 addresses 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.

## 2. GENERAL CONCEPTS

The following concepts are important in the development and setting of harmonized specifications. They are not universally applicable, but each should be considered in particular circumstances. This guideline presents a brief definition of each concept and an indication of the circumstances under which it may be applicable. Generally, proposals to implement these concepts should be justified by the applicant and approved by the appropriate regulatory authority before being put into effect.

### 2.1. Periodic or skip testing

Periodic or skip testing is the performance of specified tests at release on pre-selected batches and / or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation. This concept may be applicable to, for example, residual solvents and microbiological testing, for solid oral dosage forms. It is recognized that only limited data may be available at the time of submission of an application (see section 2.5). This concept should therefore generally be implemented post-approval. When tested, any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authority(ies). If these data demonstrate a need to restore routine testing, then batch by batch release testing should be reinstated.

### 2.2. Release vs. shelf-life acceptance criteria

The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only; it pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf-life. Examples where this may be applicable include assay and impurity (degradation product) levels. In Japan and the United States, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria. Thus, in these regions, the regulatory acceptance criteria are the same from release throughout shelf-life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf-life. In the European Union there is a regulatory requirement for distinct specifications for release and for shelf-life where different.

### 2.3 In-process tests

In-process tests, as presented in this guideline, are tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

In-process tests which are only used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores which will be coated and individual tablet weights, are not included in the specification.

Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification. However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to finished product.

### 2.4. Design and development considerations

The experience and data accumulated during the development of a new drug substance or product should form the basis for the setting of specifications. It may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

- microbiological testing for drug substances and solid dosage forms which have been shown during development not to support microbial viability or growth (see Decision Trees #6 and #8).
- extractables from product containers where it has been reproducibly shown that either no extractables are found in the drug product or the levels meet accepted standards for safety.
- particle size testing may fall into this category, may be performed as an in-process test, or may be performed as a release test, depending on its relevance to product performance.
- dissolution testing for immediate release solid oral drug products made from highly water soluble drug substances may be replaced by disintegration testing, if these products have been demonstrated during development to have consistently rapid drug release characteristics (see Decision Trees #7(1) through #7(2)).

### 2.5. Limited data available at filing

It is recognized that only a limited amount of data may be available at the time of filing, which can influence the process of setting acceptance criteria. As a result it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (example: acceptance limits for a specific impurity). The basis for the acceptance criteria at the time of filing should necessarily focus on safety and efficacy.

When only limited data are available, the initially approved tests and acceptance criteria should be reviewed as more information is collected, with a view towards possible modification. This could involve loosening, as well as tightening, acceptance criteria as appropriate.

### 2.6 Parametric release

Parametric release can be used as an operational alternative to routine release testing for the drug product in certain cases when approved by the regulatory authority. Sterility testing for terminally sterilized drug products is one example. In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, e.g., temperature, pressure,

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