1.12

ICH Q6A Guideline

Specifications: Test Procedures and Acceptance Criteria for

New Drug Substances and New Drug Products

Comments for its application

Specifications: Test Procedures and Acceptance Criteria ICH Q6A

1.1 Objective of the Guideline

Establishment of a single set of global specifications for new drug substances and products.

Guidance on the setting and justification of acceptance criteria and the selection of test procedures.

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.

Conformance to specifications means listed acceptance criteria are met.

Specifications are binding quality standard that are agreed to between the appropriate governmental regulatory agency and the applicant.

Specifications are based upon *thorough product characterisation* during *development.*

Specifications are chosen to confirm the quality of the drug substance and drug product 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 products is determined by their:

- design
- development
- in-process controls
- GMP controls
- process validation
- specifications applied to them throughout development and manufacture.

The guideline addresses specifications, e.g. those tests, procedures and acceptance criteria used to *assure the quality at release* and *during shelf life*.

The guideline addresses only the *marketing approval* of new drug products but *not* the clinical research stages of drug development.

1.3 Scope of the Guideline

❒ **Acceptance criteria:**

- universal acceptance criteria established for all drug substances and products,
- specific to individual drug substance and/or dosage forms.

❒ **The guideline covers:**

- solid dosage forms
- liquid dosage forms
- parenterals (small and large volume).

2. General Concepts

2.1 Periodic/Skip Testing

Performance of specified tests at release on pre-selected batches and/or at predetermined intervals.

This less than full schedule of testing should be justified and presented to the regulatory authority prior to implementation.

Examples for solid dosage forms:

- dissolution
- residual solvents
- microbiological testing.

This concept may be implemented post-approval in accordance with GMP, if sufficient data are available.

2.2 Release vs. Shelf Acceptance Criteria

Applicable only to drug products.

More restrictive criteria for release than for shelf life

- assay
- impurity (degradation products).

In USA and Japan release specifications only in house criteria, in the EU regulatory requirements for distinct specifications for release and for shelf life.

2.3 In-process Tests

- In-process tests which are used for the purpose of adjusting process parameters within an operating range, e.g. hardness and friability, are not included in the specifications.

- Test conducted during manufacturing process where acceptance criteria is identical or tighter than release requirements, e.g. pH of solution may be used to satisfy specification requirements when
  the test is included in the specification.

2.4 Design and Development Considerations

Examples for skip testing

The *experience* and *data accumulated* during the development of a new drug substance or product should form the *basis* for setting specifications.

It may be possible to propose *excluding* or replacing certain tests on this basis:

- Microbiological testing for drug substances and solid dosage forms not show support for microbial viability or growth.

- Extractables from product containers. No extractable found or levels met accepted standard for safety.

- Particle size:

  - in-process or
  - release test

  depending on relevance to product performance.

- Dissolution testing versus disintegration testing for immediate release solid oral drug products.

2.5 Limited Data Available at Filing

If only limited amount of data may be available it may be necessary to propose revised acceptance criteria as additional experience is gained during manufacture, e.g. specific impurities. Basis at the time of filing: safety and efficacy.

2.6 Parametric release

Parametric release as operational alternative to routine release testing.

Sterility testing based on monitoring temperature and pressure during terminal sterilisation phase. If parametric release is performed, the attribute which is indirectly controlled, e.g. sterility, together with a reference to the associated test procedure should be included in the specifications.

2.7 Alternative Procedures

Alternative procedures or those which may be used if *comparable* or *superior* to the official procedure.

Examples:

- Tablets *no degradation* during manufacture, spectrophotometric procedure for release instead of chromatographic.

- Chromatographic procedure used to demonstrate compliance with acceptance criteria *during* shelf life.

2.8 Pharmacopoeial tests and acceptance criteria

Whenever appropriate pharmacopoeial methods should be utilised.

A harmonised specification is possible only if the procedure and acceptance criteria defined are acceptable to regulatory authorities in all regions.

The full utility of this guideline is dependent on the successful completion of harmonisation of pharmacopoeial procedure for several attributes commonly considered in the specification for new drug substances and products.

To signify the harmonised status of these procedure, the pharmacopoeias have agreed to include a statement in their respective texts which indicates that the procedure and the acceptance criteria from all three pharmacopoeias are considered to be equivalent and are therefore interchangeable.

2.10 Impact of Drug Substance on Drug Product Specifications

Not necessary to test drug product for synthesis impurities which are controlled in the drug substance and are not degradation products.

2.11 Reference Standard

Reference standard is substance prepared for use as standard for

- assay
- identification
- purity test.

Substance either

- the new drug substance
- or a known impurity.

Quality appropriate to its use.

Purity should be measured by a quantitative procedure.

3. Guidelines

3.1 Specifications: Definition and Justification

3.1.1 Definition of Specifications

- List of tests,
- references to analytical procedures,
- appropriate acceptance criteria.

In addition a specification may list

- in-process tests
- periodic (skip) tests
- other tests not conducted on a batch to batch basis.

Specifications are binding quality standards.

Applicant should specify, which tests are done routinely, which not, justification.

Specification changes after approval may need prior approval by regulatory authority.

3.1.2 Justification of Specifications

Justification required for

- each procedure,
- each acceptance criterion included in the specification.

Justification should refer to:

- relevant development data,
- pharmacopoeial standards,
- test data of batches used in toxicology and clinical studies,
- results from accelerated and long term stability studies,
- reasonable range of expected analytical and manufacturing variability.

3.1.2 Justification of Specifications

Setting and justifying specifications by

- batches from:
  - primary stability
  - scale-up
  - validation.
- Multiple manufacturing sites:

  Data from these sites in establishing the initial tests and acceptance criteria.

  If data from a single representative manufacturing site are used in setting tests and acceptance criteria, product manufactured at all sites should comply with these criteria.

Presentation of test results in graphic format may be helpful in justifying individual acceptance criteria.

Justification for exclusion of a test from the specification should be based on development data and process validation data (where available). If only limited data available initially approved test and acceptance criteria should be reviewed.

- loosening
- tightening.

3.2 Universal Tests/Criteria

3.2.1 New Drug Substances

The following tests and acceptance criteria generally applicable:

❒ **Description**

Qualitative statement: state (e.g. solid, liquid), colour.
If changes during storage, change should be investigated and appropriate action taken.

❒ **Identification**

Discrimination between compounds of closely related structure which are likely to be present.

Identification should be specific:

- infrared spectroscopy or
- HPLC/UV diode array or
- HPLC/MS or
- GC/MS

If salt, identification of individual ions.

❒ **Assay**

- specific, stability indicating
- non specific + test for impurities.

3.2.1 New Drug Substances

❒ Impurities

- organic
- inorganic
- residual solvents.

Establishing acceptance criteria for a specified impurity. Decision tree No. 1.

- Mean of relevant batches (development, pilot and scale-up) +
- upper confidence limit (three times standard deviation sd)

Example:

0.1, 0.05, 0.12, 0.07, 0.09, 0.08:
Mean: 0.09, sd: 0.024, 3 x sd: 0.07, mean + 3 x sd: 0.16

≤ qualified level: acceptance criteria
> qualified level: acceptance criteria = qualified level or new qualified level.

If impurity is decomposition product, increase during storage should be added. At the time of filing it is unlikely that sufficient data will be available to assess process consistency Therefore it is inappropriate to establish acceptance criteria which tightly encompass the batch data at time of filing.

3.2.2 New Drug Products

❒ Description

Qualitative description (size, shape, colour). If *change* during storage appropriate action should be taken. Acceptance criteria should include *final* acceptance criteria. If colour changes during storage quantitative procedure may be appropriate.

❒ Identification

Should be able to discriminate between compounds of closely related structure which are likely to be present.

- Infrared or
- HPLC/UV diode array.

❒ **Assay**

Specific, stability-indicating assay. Results of *CU* can be used, if the methods used are also appropriate as assays.

3.2.2 New Drug Products

❒ **Impurities**

- organic
- inorganic
- residual solvents.

Degradation products should be monitored.

Acceptance limits:

- individual specified degradation products,
  - identified,
  - unidentified,
- total degradation products.

Process impurities are not included in total impurities limit.

If specific formulation does not degrade under specific storage conditions, degradation product testing may be reduced or eliminated upon approval.

Meaningful limits on degradation products: Decision tree No. 2.

- Data generated during development.+
- Degradation during manufacture +
- Estimation of maximum increase in degradation at shelf life using data from relevant accelerated and long term stability studies.

At the time of filing it *is* unlikely that sufficient data will be available to assess process consistency.

3.3 Specific tests/criteria

3.3.1 New Drug Substances

❒ **Physico-chemical properties**

- pH of aqueous solution
- melting point/range
- refractive index

Tests performed should be determined by physical nature and by its intended use.

❒ **Particle size**

significant effect on:

- dissolution rate
- bioavailability/or stability

In such cases testing for particle size distribution and acceptance criteria.

Decision tree No. 3

No particle size acceptance criterion:

- drug substance is dissolved during manufacture
- solution dosage form
- not critical to product processability, stability, content uniformity.

3.3.1 New Drug Substances

▪

❒ **Polymorphic forms**

If solid state forms, polymorphs or solvates, differ in physical properties which have shown to affect drug product *performance*, *bioavailability* or *stability*, then the appropriate state should be specified.

- **Analytical Techniques**

  - melting point including hot-stage microscopy
  - solid state IR
  - X-ray powder diffraction
  - thermal analysis procedures like DSC, TGA, DTA
  - raman spectroscopy
  - solid state NMR.
  - optical microscopy

Decision trees No. 4.1 -4.3

Polymorphism *screen* on drug substances should be conducted.

Acceptance criteria for drug substance of drug product affected concerning:

- safety
- performance
- efficacy.

It is very difficult to measure polymorphic changes in drug products. A surrogate test, e.g. dissolution, can generally be used to monitor product performance. Polymorphic content should be only used as a test and acceptance criterion of last resort. (These impurities not in the impurity guidelines)

3.3.1 New Drug Substances

❒ **Tests for chiral new drug substance:**

- impurities: single enantiomer control of other enantiomer should be considered, but higher limits.
- assay: enantioselective determination part of specification
  - chiral assay procedure or
  - combination of achiral assay together with enantiomeric impurity test.
- identity: distinguishing single enantiomer from opposite enantiomer
  racemate: verifying racemic nature and distinguishing it from either enantiomer

❒ **Drug products:**

- degradation product: Control of other enantiomer if it has been shown to be degradation product.
- assay: Achiral assay may be sufficient if enantiomer is not decomposition product.
  If possible chiral assay or achiral assay + impurity other enantiomer.
- identity: Verifying presence of correct enantiomer or racemate.

3.3.1 New Drug Substances

❒ **Water content:**

- hygroscopic
- degraded by moisture
- a stoichiometric hydrate.

Acceptance criteria justified with effect of moisture.

Preferred: Karl Fischer, possible loss on drying.

❒ **Inorganic impurities**

Acceptance criteria should follow pharmacopoeial precedents.

❒ **Microbial limits**

- total count of aerobic microorganisms
- total count of yeasts and molds
- absence of specific objectionable bacteria

Decision tree No. 6.

3.3.2 New Drug Products

3.3.2.1 Tablets coated or uncoated, hard capsules

❒ **Disintegration**

- Highly soluble throughout physiological pH range. Solubility at 37°C ± 0.5°C, dose + solubility < 250 ml, pH 1.2 - 6.8.

- Rapidly dissolving drugs:

  - Dissolution > 80 % in 15 minutes at pH 1.2, 4.0, 6.8
  - Relationship between disintegration and dissolution respectively
  - disintegration more discriminating than dissolution.

  → Disintegration acceptance criteria are established.

Dissolution may not be necessary or proposed as a skip test.

3.3.2.1 Tablets coated or uncoated, hard capsules

❒ **Dissolution**

- Immediate release

  - single point
  - Appropriate test conditions

  Changes in dissolution affect significantly bioavailability:
  → Test conditions should distinguish batches with unacceptable bioavailability.

  Changes in formulation or manufacturing variables affect dissolution:
  → dissolution test conditions should distinguish these changes

  Dissolution affects significantly bioavailability:
  → Acceptance criteria should be set to reject batches with unacceptable bioavailability
  Otherwise:
  Establish test conditions and acceptance criteria which pass all clinical batches with allowance for analytical and stability variability.

3.3.2.1 Tablets coated or uncoated, hard capsules

❒ Dissolution

- Modified release

  Appropriate test conditions and sampling procedures should be established

- Extended-release
  - Multiple point acceptance criteria may be necessary.
  - Bioavailability are available for batches with different release rates.
  - In vitro/in vivo relationship can be established -(modifying in vitro test conditions if appropriate).
  - Use the in vitro/in vivo correlation along with appropriate batch data.

Otherwise:
Use all available stability, clinical and bioavailability data
to establish appropriate acceptance criteria.

The permitted variability in release rate at any given time point should not exceed a numerical difference of ± 10 % of the labelled content, e.g. 50 ± 10 % means 40 % to 60 %.

- Delayed release:
  Two stage testing (using different media in succession or in parallel).

Decision trees No. 7.1 - 7.4

3.3.2.1 Tablets coated or uncoated, hard capsules

❒ **Hardness/friability**

If critical impact on drug quality acceptance criteria should be established.

❒ **Uniformity of dosage units**

❒ **Uniformity of content and uniformity of mass:**

pharmacopoeial procedure

❒ **Water content**

If appropriate: Preferred Karl Fischer titration, loss on drying may be acceptable.

❒ **Microbial limits**

It is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known not to carry significant risk of microbial contamination.
Skip testing may be appropriate

Acceptance criteria:

- total count of aerobic microorganisms
- total count of yeasts and molds
- absence of specific objectionable bacteria.

With acceptable scientific justification, possible no microbial limit testing for solid oral dosage forms.
Decision tree No. 8

3.3.2.2. Oral Liquids

❒ **Uniformity of dosage units**

Acceptance criteria for

- weight variation,
- fill volume
- and/or uniformity of fill

according to pharmacopoeial procedures.

Dosage unit is considered to be the typical dose taken by the patient, measured directly or calculated. If dispensing equipment, this should be used to measure the dose.

❒ **pH**

Acceptance criteria where applicable and proposed range justified.

❒ **Microbial limits**

Skip testing may be appropriate approach.
For powders intended for reconstitution as oral liquids it may be possible to propose *no* microbial limit testing with acceptable *scientific* justification.

Acceptance criteria as for solid dosage forms.

3.3.2.2. Oral Liquids

❒ **Antimicrobial preservative content**

- Acceptance criteria based on levels to maintain microbiological product quality throughout shelf life.
- The lowest specified concentration should be controlled by antimicrobial

preservative
effectiveness test.

- Antimicrobial preservative effectiveness. should be demonstrated during development, scale-up, throughout the shelf life.

❒ **Antioxidant preservative content**

- Release testing should be performed,
- shelf life testing may be unnecessary where justified by development and stability data.

❒ **Extractables**

Where development and stability data show no significant evidence of extractables elimination of this test may be proposed.

Where data demonstrate need acceptance criteria for oral solutions:

- rubber stopper
- cap liner
- plastic bottle

Data should be collected as early in development process as possible.

3.3.2.2. Oral Liquids

❒ **Dissolution**

For insoluble drug substance for oral suspensions, dry powder products for resuspension,
dissolution testing and acceptance criteria.

❒ **Particle size distribution**

Quantitation acceptance criteria and analytical procedure may be appropriate.

Development data should be considered for either *dissolution procedure* or *particle size distribution*. Acceptance criteria should include:

- acceptable particle size distribution in terms of
  percent of total particles in given size ranges:

Mean, upper and/or lower particle size limits should be well defined.

3.3.2.2. Oral Liquids

❒ **Redispersibility**

Oral suspension:

Shaking, mechanical or manual,
time to achieve resuspension

Data from development may justify:

- skip lot testing or
- elimination from specification.

❒ **Reconstitution time**

Dry powder which require reconstitution
- skip lot testing or
- elimination.

❒ **Water content**

Oral products requiring reconstitution

- loss on drying.

3.3.2.3 Parenteral Drug Products

❒ Uniformity of dosage units

- weight variation,
- fill volume
- uniformity of fill

according to pharmacopoeial procedure.

❒ **pH**

Where applicable, acceptance criteria and range justified.

❒ **Sterility**

All parenteral products

Where data generated during development and validation justify parametric release (terminally sterilised drug products).

- Endotoxines
  Limulus amoebocyte test.

- Pyrogens

  Alternative to endotoxine testing where justified.

3.3.2.3 Parenteral Drug Products

.

❒ **Particulate matter**

- limits for visible particulates (foreign matter)
- and/or clarity of solution
- sub-visible particulate.

❒ **Water content**

- Non-aqueous parenterals,
- parenterals for reconstitution.

Acceptance criterion for water content, loss on drying (Karl Fischer Titration).

❒ **Antimicrobial preservative content**

Lowest specified concentration demonstrated by antimicrobial preservative effectiveness test. Antimicrobial preservative effectiveness should be demonstrated during development, scale-up, throughout shelf life.

❒ **Extractables**

Where development and stability data show no significant evidence of extractables, elimination of this test may be proposed.
Otherwise acceptance criteria have to be established.

❒ **Functionality testing of delivery system**

For pre-filled syringes, autoinjector cartridges or equivalent test procedures and acceptance criteria should be established concerning functionality.