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

ICH Guidelines Q6A (www.ich.org)

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Definitions and general concepts

Specifications and acceptance criteria

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria.

It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

- Example:
- Assay acceptance criteria 90-110%
- 110.5%-- ☾ pass or fail??

Specifications and acceptance criteria

Example: Drug product specifications

Attribute	Acceptance Criteria (typical values)	Analytical Procedure (for example)
Identity	Matches Standard	IR or HPLC/UV
Appearance	Color, Imprint	Visual
Assay	90-110%	HPLC
Dose Uniformity	Statistical Criterion (USP)	HPLC or Weight
Release from Dosage Form	80% in 15 or 30 minutes	Stirred Aqueous Vessel
Impurities (Related Substances)	<1% to few %	HPLC
Microbial Limits Or Sterility	# of total aerobes and fungi per gram Pathogen (-)	Growth in special media
Water Content	Few %	Chemical or wgt. loss
Preservative Content	NLT 75% of Initial	HPLC

Specifications and acceptance criteria

Example: Drug product specifications

Table 2: Example of solid oral drug product specifications for early development.

Test Name	Test Method	Acceptance Criteria
Description Shape Colour	Visual	Product specific shape and colour
Identity by HPLC	HPLC	Consistent with reference*
Identity by UV	HPLC–PDA	Consistent with reference*
Assay by HPLC (% label claim)	HPLC	90.0–110.0%*
Degradation products by HPLC Individual unspecified Total	HPLC	 ≤1.0%* ≤5.0%*
Dissolution	HPLC or UV	Report*
Disintegration	USP<701>	≤15 min
Uniformity of dosage units	HPLC or weight variation	Corresponds to USP<905>*

Specifications and acceptance criteria

- "**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.

Specifications and acceptance criteria

- Specifications should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

- The quality of drug substances and drug products is determined by :

1. their design,
2. development,
3. in-process controls,
4. GMP controls,
5. process validation, and
6. by specifications applied to them throughout development and manufacture.

Definitions

Specific test: A test which is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

Universal test: A test which is considered to be potentially applicable to all new drug substances, or all new drug products; e.g., appearance, identification, assay, and impurity tests.

Definitions

New drug substance: The designated therapeutic moiety, which has not previously been registered in a region or Member State (also referred to as a new molecular entity or new chemical entity).

- It may be a complex, simple ester, or salt of a previously approved drug substance.

New drug product: A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., which has not previously been registered in a region or Member State, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

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GENERAL CONCEPTS

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.

GENERAL CONCEPTS

Periodic or Skip Testing

- This concept should 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.

GENERAL CONCEPTS

Release Acceptance Criteria 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.
-

GENERAL CONCEPTS

Release Acceptance Criteria vs. Shelf-life Acceptance Criteria

- In Japan and the United States, this concept may only be applicable to in-house criteria, and **not** to the regulatory release criteria.
- 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.

GENERAL CONCEPTS

In-process Tests

- **In-process tests**, are tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal series 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.

GENERAL CONCEPTS

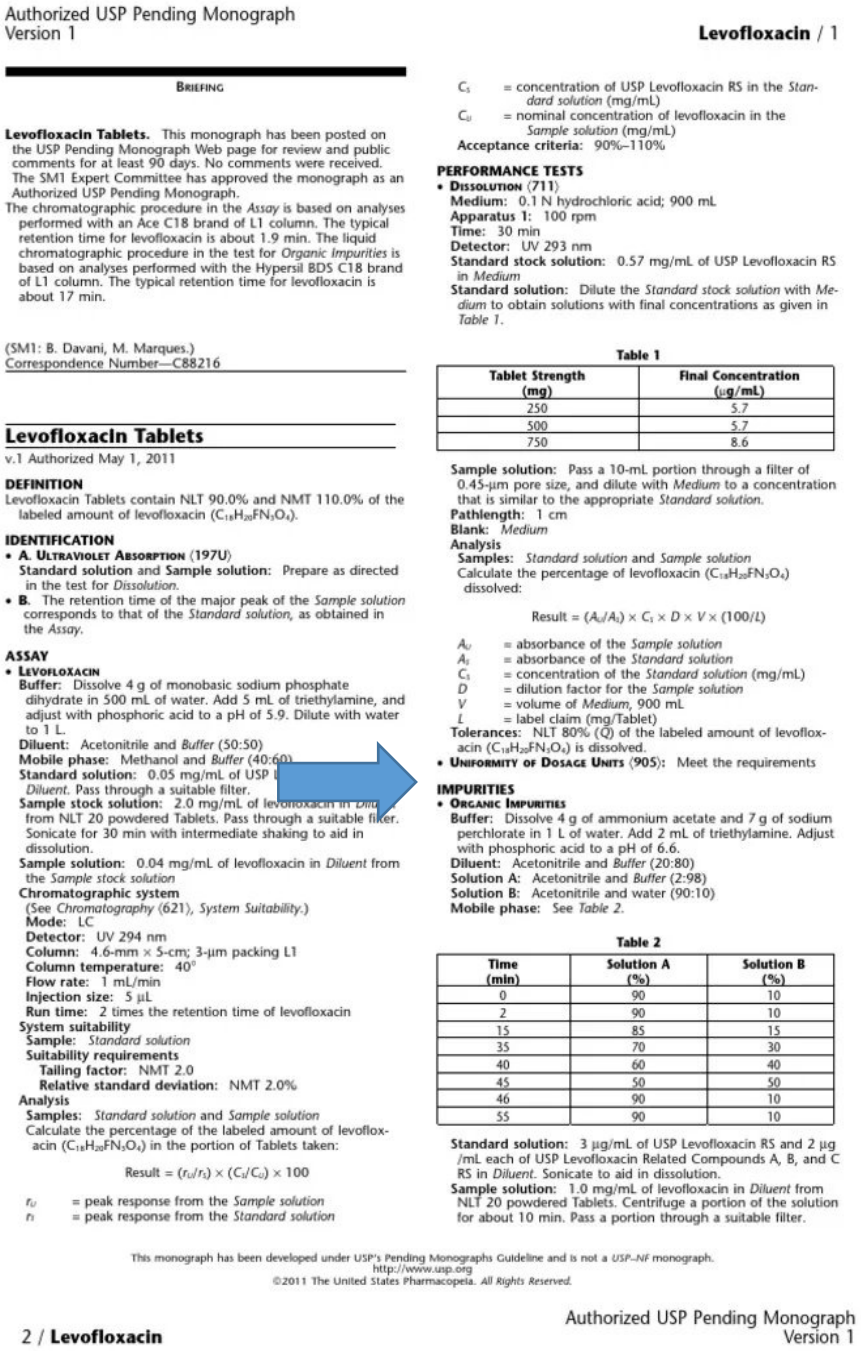
In-process Tests

- 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.

GENERAL CONCEPTS

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).



Authorized USP Pending Monograph
Version 1

Levofloxacin / 1

BRIEFING

Levofloxacin Tablets. This monograph has been posted on the USP Pending Monograph Web page for review and public comments for at least 90 days. No comments were received. The SM1 Expert Committee has approved the monograph as an Authorized USP Pending Monograph.
The chromatographic procedure in the *Assay* is based on analyses performed with an Ace C18 brand of L1 column. The typical retention time for levofloxacin is about 1.9 min. The liquid chromatographic procedure in the test for *Organic Impurities* is based on analyses performed with the Hypersil BDS C18 brand of L1 column. The typical retention time for levofloxacin is about 17 min.

(SM1: B. Davani, M. Marques.)
Correspondence Number—C88216

Levofloxacin Tablets

v.1 Authorized May 1, 2011

DEFINITION
Levofloxacin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of levofloxacin ($C_{18}H_{20}FN_3O_4$).

IDENTIFICATION
- **A. ULTRAVIOLET ABSORPTION ⟨197U⟩**
  Standard solution and **Sample solution:** Prepare as directed in the test for *Dissolution*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **LEVOFLOXACIN**
  Buffer: Dissolve 4 g of monobasic sodium phosphate dihydrate in 500 mL of water. Add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 5.9. Dilute with water to 1 L.
  Diluent: Acetonitrile and *Buffer* (50:50)
  Mobile phase: Methanol and *Buffer* (40:60)
  Standard solution: 0.05 mg/mL of USP L
  Diluent. Pass through a suitable filter.
  Sample stock solution: 2.0 mg/mL of levofloxacin in *Dilu*
  from NLT 20 powdered Tablets. Pass through a suitable filter. Sonicate for 30 min with intermediate shaking to aid in dissolution.
  Sample solution: 0.04 mg/mL of levofloxacin in *Diluent* from the *Sample stock solution*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 294 nm
  Column: 4.6-mm × 5-cm; 3-µm packing L1
  Column temperature: 40°
  Flow rate: 1 mL/min
  Injection size: 5 µL
  Run time: 2 times the retention time of levofloxacin
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of levofloxacin ($C_{18}H_{20}FN_3O_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Levofloxacin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of levofloxacin in the *Sample solution* (mg/mL)
Acceptance criteria: 90%–110%

PERFORMANCE TESTS
- **DISSOLUTION ⟨711⟩**
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 1: 100 rpm
  Time: 30 min
  Detector: UV 293 nm
  Standard stock solution: 0.57 mg/mL of USP Levofloxacin RS in *Medium*
  Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain solutions with final concentrations as given in *Table 1*.

Table 1

Tablet Strength (mg)	Final Concentration (µg/mL)
250	5.7
500	5.7
750	8.6

Sample solution: Pass a 10-mL portion through a filter of 0.45-µm pore size, and dilute with *Medium* to a concentration that is similar to the appropriate *Standard solution*.
Pathlength: 1 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of levofloxacin ($C_{18}H_{20}FN_3O_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times V \times (100/L)$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
Tolerances: NLT 80% (Q) of the labeled amount of levofloxacin ($C_{18}H_{20}FN_3O_4$) is dissolved.
- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES
- **ORGANIC IMPURITIES**
  Buffer: Dissolve 4 g of ammonium acetate and 7 g of sodium perchlorate in 1 L of water. Add 2 mL of triethylamine. Adjust with phosphoric acid to a pH of 6.6.
  Diluent: Acetonitrile and *Buffer* (20:80)
  Solution A: Acetonitrile and *Buffer* (2:98)
  Solution B: Acetonitrile and water (90:10)
  Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	90	10
2	90	10
15	85	15
35	70	30
40	60	40
45	50	50
46	90	10
55	90	10

Standard solution: 3 µg/mL of USP Levofloxacin RS and 2 µg /mL each of USP Levofloxacin Related Compounds A, B, and C RS in *Diluent*. Sonicate to aid in dissolution.
Sample solution: 1.0 mg/mL of levofloxacin in *Diluent* from NLT 20 powdered Tablets. Centrifuge a portion of the solution for about 10 min. Pass a portion through a suitable filter.

GENERAL CONCEPTS

Limited Data Available at Filing

- 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.

GENERAL CONCEPTS

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, and time during the terminal sterilization phase(s) of drug product manufacturing.
- These parameters can generally be more accurately controlled and measured, so that they are more reliable in predicting sterility assurance than is end-product sterility testing.

GENERAL CONCEPTS

Parametric Release

- Appropriate laboratory tests (e.g., chemical or physical indicator) may be included in the parametric release program.
- It is important to note that the sterilization process should be adequately validated before parametric release is proposed and maintenance of a validated state should be demonstrated by revalidation at established intervals.
- When parametric release is performed, the attribute which is indirectly controlled (e.g., sterility), together with a reference to the associated test procedure, still should be included in the specifications.

GENERAL CONCEPTS

Alternative Procedures

- Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is comparable or superior to the official procedure.

Example:

- For tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic.
- However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf-life of the product.

GENERAL CONCEPTS

Pharmacopoeial Tests and Acceptance Criteria

- References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures **should be** utilized.

Evolving Technologies

- New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

GENERAL CONCEPTS

Impact of Drug Substance on Drug Product Specifications

- In general, it should not be necessary to test the drug product for quality attributes uniquely associated with the drug substance.

Example:

- It is normally not considered necessary to test the drug product for synthesis impurities which are controlled in the drug substance and are not degradation products.

GENERAL CONCEPTS

Reference Standard

- **A reference standard, or reference material**, is a substance prepared for use as the standard in an assay, identification, or purity test.
- It should have a quality appropriate to its use.
- It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing.
- For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and / or controlled, and purity should be measured by a quantitative procedure.

Guidelines

Specifications

- A specification may list, in addition to release tests in-process tests and periodic (skip) tests,.
- In such cases the applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency.
- In this situation, the drug substance and / or drug product should meet the acceptance criteria if tested.

Justification of Specifications

- When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included.
- The justification should refer, as appropriate, to:
  - relevant development data,
  - pharmacopoeial standards,
  - test data for drug substances and drug products used in toxicology and clinical studies,
  - results from accelerated and long term stability studies.

Justification of Specifications

- Test results from stability and scale-up / validation batches, with emphasis on the primary stability batches, **should be considered in setting and justifying specifications**.
- It should be noted that changes in the specification after approval of the application may need prior approval by the regulatory authority.

Universal Tests			
New Drug Substances	**New Drug products**		
Description			
Identification			
Assay			
Impurities			
Specific Tests			
New Drug Substances	**New Drug products**		
	Solid oral drug products	**Oral liquids**	**Parenteral Drug Products**
Water content	Water content	Water content	Water content
Particle size		Particle size distribution	Particle size distribution
			Particulate matter
	Uniformity of dosage units	Uniformity of dosage units	Uniformity of dosage units
	Dissolution	Dissolution	
	Disintegration		
Physicochemical properties		pH	Osmolarity
Polymorphic forms	Hardness/friability		
		Extractables	
Tests for chiral new drug substances			
Microbial limits	Microbial limits	Microbial limits	Sterility
		Antimicrobial preservative content	Antimicrobial preservative content
			Endotoxins/Pyrogens
		Redispersibility	Redispersibility
Inorganic impurities			
		Reconstitution time	Reconstitution time
		Antioxidant preservative content	Extractables

Universal Tests / Criteria : New Drug Substances & Products

a) ***Description***:

For drug substance: a qualitative statement about the state (e.g. solid, liquid) and color of the new drug substance.

For drug product: A qualitative description of the dosage form should be provided (e.g., size, shape, and color).

- If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

Universal Tests / Criteria : New Drug Substances & products

b) ***Identification***

- Identification testing should optimally be able to discriminate between compounds of closely related structure which are likely to be present.
- Identification tests should be specific for the new drug substance, e.g., infrared spectroscopy.
- Identification solely by a single chromatographic retention time, for example, is not regarded as being specific.

Universal Tests / Criteria : New Drug Substances

b) Identification

- However, the use of two chromatographic procedures, where the separation is based on different principles or a combination of tests into a single procedure, such as **HPLC/UV diode array**, **HPLC/MS**, or **GC/MS** is generally acceptable.
- If the new drug substance is a salt, identification testing **should be specific for the individual ions**. An identification test that is specific for the salt itself should suffice.

e.g. to distinguish between diclofenac sodium and diclofenac potassium

Universal Tests / Criteria : New Drug Substances

b) Identification

- New drug substances which are optically active may also need specific identification testing or performance of a chiral assay.

Examples:
L-Dopa (D-dopa is inactive)
Levofloxacin is the active optical isomer of ofloxacin
Levocetirizine is the active enantiomer of cetirizine

Identification testing for drug product should establish the identity of the new drug substance(s) in the new drug product

Universal Tests / Criteria : New Drug Substances and products

*c) **Assay***

A specific, stability-indicating procedure should be included to determine the content of the drug in new drug substance and new drug products.

In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance/product and quantitation of impurities.

- Results of content uniformity testing for new drug products can be used for quantitation of drug product strength, if the methods used for content uniformity are also appropriate as assays.

Universal Tests / Criteria : New Drug Substances and products

c) ***Assay***

In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity.

For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable test for impurities should be used.

- A specific procedure should be used when there is evidence of excipient interference with the non-specific assay.

Universal Tests / Criteria : New Drug Substances

*d) **Impurities:***

Impurities in new drug subsances can be classified into the following categories (ICH Q3A):

1. Organic impurities
   - Starting materials
   - By-products
   - Intermediates
   - Degradation products
   - Reagents, ligands and catalysts
2. Inorganic impurities
   - Reagents, ligands and catalysts
   - Heavy metals or other residual metals
   - Inorganic salts
   - Other materials (e.g., filter aids, charcoal)

Universal Tests / Criteria : New Drug Substances

d) ***Impurities:***

3. Residual solvents

Class 1 solvents: Solvents to be avoided

- Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
- E.g. Benzene, CCl4

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.
- E.g. Acetonitrile, Chloroform, Methanol, Dichloromethane, hexane

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 permitted daily exposure (PDE)s of 50 mg or more per day.
- E.g. Acetic acid, Ethanol, Ethyl acetate, Dimethyl sulfoxide, Acetone

Universal Tests / Criteria : New Drug products

d) impurities:

- Organic and inorganic impurities (degradation products) and residual solvents are included in this category.
- Organic impurities arising from degradation of the new drug substance and impurities that arise during the manufacturing process for the drug product should be monitored in the new drug product.
- Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit.
- However, when a synthesis impurity is also a degradation product, its level should be monitored and included in the total degradation product limit.

Universal Tests / Criteria : New Drug products

d) impurities:

- Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products.
- When it has been conclusively demonstrated via appropriate analytical methodology, that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application:

- ☾ degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

Specific Tests / Criteria : New Drug Substances

The following tests may be considered on a case by case basis for drug substances.

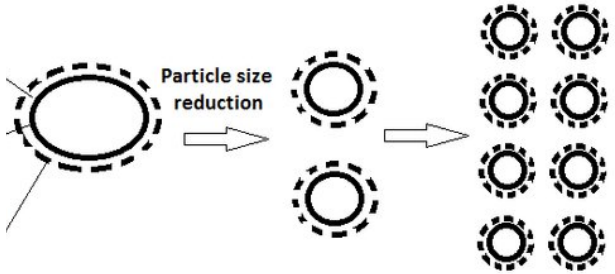
a) Physicochemical properties:

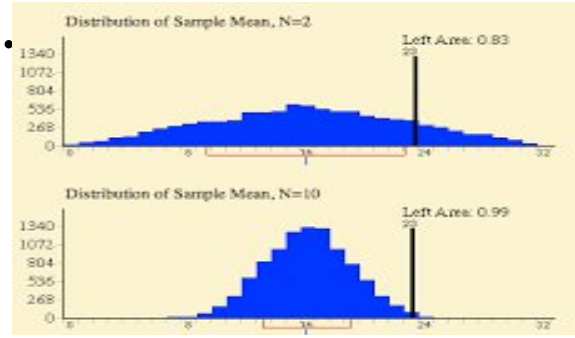
e.g. pH of an aqueous solution, melting point / range, and refractive index.

b) Particle size:

For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability.

In such instances, procedure for testing of size distribution and acceptance criteria should be provided.

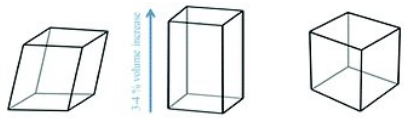




Specific Tests / Criteria : New Drug Substances

c) Polymorphic forms:

In cases where different crystal forms exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified.



Example: Part of Chloramphenicol monograph in USP

Melting range ⟨741⟩: between 149° and 153°.

Specific rotation ⟨781S⟩: between +17.0° and +20.0°.

Test solution: 50 mg, undried, per mL, in dehydrated alcohol.

Crystallinity ⟨695⟩: meets the requirements.

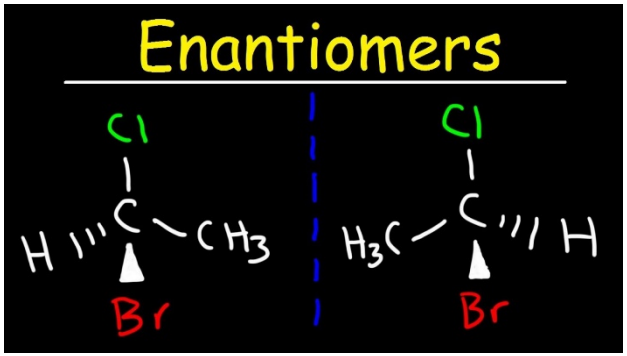
Bacterial endotoxins ⟨85⟩—Where Chloramphenicol is intended for use in preparing injectable dosage forms, it contains

Specific Tests / Criteria : New Drug Substances

d) Tests for chiral new drug substances:

For a drug substance developed as a single enantiomer:

1. The identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture.
2. An enantioselective determination of the drug substance should be part of the specification.
3. Control of the other enantiomer should be considered in the same manner as for other impurities.



Specific Tests / Criteria : New Drug Substances

e) ***Water content***: This test is important in cases where the new drug substance is known to be:

1. hygroscopic
2. degraded by moisture
3. is a hydrate.

The acceptance criteria may be justified with data on the effects of hydration or moisture absorption.

In some cases, a Loss on Drying procedure may be considered adequate; however, a detection procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

Specific Tests / Criteria : New Drug Substances

f) Inorganic impurities:

The need for inclusion of tests and acceptance criteria for inorganic impurities (e.g., catalysts) should be studied during development and based on knowledge of the manufacturing process.

Procedures and acceptance criteria for:

A. sulfated ash / residue on ignition should follow pharmacopoeial precedents;

B. other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.

Specific Tests / Criteria : New Drug Substances

g) ***Microbial limits***: There may be a need to specify:

- the total count of aerobic microorganisms
- the total count of yeasts and molds
- the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*).

➢ These should be suitably determined using pharmacopoeial procedures.

➢ The type of microbial test(s) and acceptance criteria should be based on the

1. nature of the drug substance,
2. method of manufacture,
3. the intended use of the drug product:
   - sterility testing may be appropriate for drug substances manufactured as sterile
   - endotoxin testing may be appropriate for drug substances used to formulate an injectable drug product.

Specific Tests / Criteria : New Drug products

- Additional tests and acceptance criteria generally should be included for **particular new drug products.**
- The ICH guidelines in Q6A presents a **representative** sample of both the drug products and the types of tests and acceptance criteria which may be appropriate.
- The specific dosage forms addressed include solid oral drug products, liquid oral drug products, and parenterals (small and large volume).
- Application of the concepts in this guideline to other dosage forms is encouraged.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

a) Dissolution:

- The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the drug product.
- immediate-release dosage forms → normally Single-point measurements
- extended-release dosage forms → multiple time point sampling should be performed
- delayed-release dosage forms → two-stage testing (using different media in succession or in parallel, as appropriate). E.g pH: 1.2, 6.8

Specific Tests / Criteria : New Drug products

Solid oral drug products:

a) Dissolution:

- For immediate-release drug products where changes in dissolution rate have been demonstrated to significantly affect bioavailability, it is desirable to develop test conditions which can distinguish batches with unacceptable bioavailability.
- If changes in formulation or process variables significantly affect dissolution and such changes are not controlled by another aspect of the specification, it may also be appropriate to adopt **dissolution test conditions** which can distinguish these changes.
- Where dissolution significantly affects bioavailability, the acceptance criteria should be set to **reject** batches with unacceptable bioavailability. Otherwise, test conditions and acceptance criteria should be established which pass clinically acceptable batches

Specific Tests / Criteria : New Drug products

Solid oral drug products:

a) Dissolution:

- For extended-release drug products, in vitro / in vivo correlation (IVIVC) may be used to establish acceptance criteria when human bioavailability data are available for formulations exhibiting different release rates.
- Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria should be established on the basis of available batch data.
- Normally, the permitted variability in mean release rate at any given time point should not exceed a total numerical difference of +/-10% of the labeled content of drug substance (i.e., a total variability of 20%: a requirement of 50 +/- 10% thus means an acceptable range from 40% to 60%), unless a wider range is supported by a bioequivalency study.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

b) Disintegration:

- For rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8) products containing drugs which are highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8), disintegration may be substituted for dissolution.
- Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution.
- In such cases dissolution testing may not be necessary.
- It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

c) Hardness/friability:

- It is normally appropriate to perform hardness and/or friability testing as an in-process control → normally not necessary to include these attributes in the specification.
- If the characteristics of hardness and friability have a critical impact on drug product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

d) Uniformity of dosage units:

- This term includes
  - the mass of the dosage form
  - the content of the active substance in the dosage form
- A pharmacopoeial procedure should be used.
- In general, the specification should include one or the other but not both.
- If appropriate, these tests may be performed in-process; however, the acceptance criteria should be included in the specification.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

d) Uniformity of dosage units:

<905> UNIFORMITY OF DOSAGE UNITS (USP monograph)

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg and ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers *and into soft capsules*			WV	WV
Others			CU	CU

Specific Tests / Criteria : New Drug products

Solid oral drug products:

e) Water content:

- A test for water content should be included when appropriate.
- The acceptance criteria may be justified with data on the effects of hydration or water absorption on the drug product.
- A detection procedure which is specific for water (e.g., Karl Fischer titration) is preferred.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

f) Microbial limits:

- Acceptance criteria should be set for:
  - the total count of aerobic microorganisms,
  - the total count of yeasts and molds,
  - the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*).
- These should be determined using **pharmacopoeial procedures**, and at a sampling frequency or time point in manufacture which is justified by data and experience.

➢ The type of microbial test(s) and acceptance criteria should be based on the

1. nature of the drug substance,
2. method of manufacture,
3. the intended use of the drug product:

Specific Tests / Criteria : New Drug products

Solid oral drug products:

f) Microbial limits:

- In general, it is advisable to test the drug product unless:
  1. its components are tested before manufacture and
  2. the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation.

➢ With acceptable scientific justification, it should be possible to propose **no microbial limit testing for solid oral dosage forms. Why???**

Specific Tests / Criteria : New Drug products

USP 2012

Table 1. Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)	Specified Microorganism(s)
Nonaqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli* (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of *Escherichia coli* (1 g or 1 mL)
Rectal use	10^3	10^2	—
Oromucosal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Gingival use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Cutaneous use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Nasal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Auricular use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Vaginal use	10^2	10^1	Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Candida albicans* (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1 patch) Absence of *Pseudomonas aeruginosa* (1 patch)
Inhalation use (special requirements apply to liquid preparations for nebulization)	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of bile-tolerant Gram-negative bacteria (1 g or 1 mL)

Specific Tests / Criteria : New Drug products

Oral liquids:

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

a) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

Specific Tests / Criteria : New Drug products

Oral liquids:

b) Uniformity of dosage units

In general, the specification should include weight variation or content uniformity test but not both.

If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used.

If appropriate, tests may be performed in-process; however, the acceptance criteria should be included in the specification.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

Specific Tests / Criteria : New Drug products

Oral liquids:

c) Microbial limits

- Skip testing may be an appropriate approach where permissible.
- With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.
- Acceptance criteria should be set for:
  1. the total count of aerobic microorganisms,
  2. the total count of yeasts and molds,
  3. the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa).

Specific Tests / Criteria : New Drug products

Oral liquids:

d) Antimicrobial preservative content:

Acceptance criteria for preservative content should be established for oral liquids needing an antimicrobial preservative.

The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Specific Tests / Criteria : New Drug products

Oral liquids:

d) Antimicrobial preservative content:

- normally performed at release → Under certain circumstances, in-process instead of release testing → however, the acceptance criteria should remain part of the specification.
- Antimicrobial preservative effectiveness should be demonstrated:
  - during development,
  - during scale up, and
  - throughout the shelf-life.

Specific Tests / Criteria : New Drug products

Oral liquids:

e) Antioxidant preservative content:

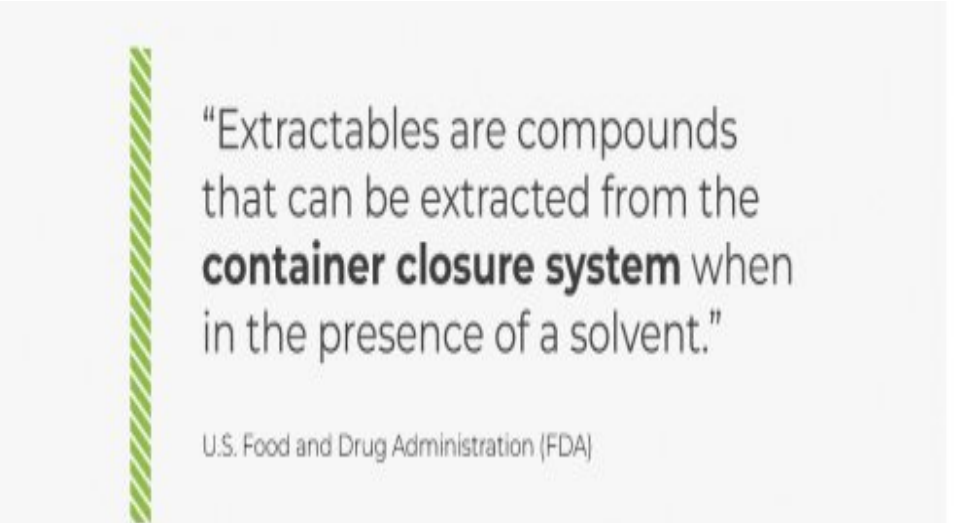
- Release testing for antioxidant content should normally be performed.
- Under certain circumstances, where justified by developmental and stability data,
  - shelf-life testing may be unnecessary,
  - in-process testing instead of release testing → the acceptance criteria should remain part of the specification.

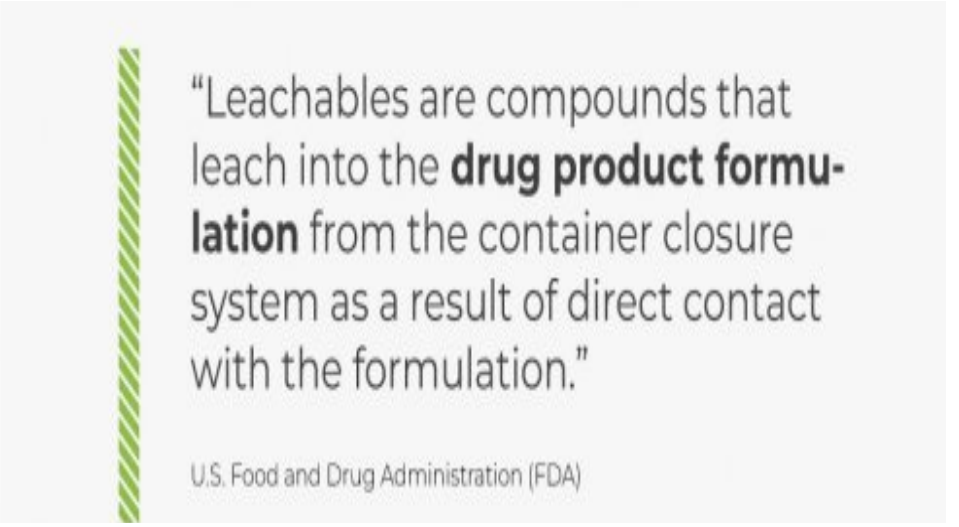
Specific Tests / Criteria : New Drug products

Oral liquids:

f) Extractables:

- Tests and acceptance criteria for extractables from the container/closure system components (e.g., rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in:
  - non-glass systems
  - glass containers with non-glass closures.





Specific Tests / Criteria : New Drug products

Oral liquids:

f) Extractables:

- Generally, where development and stability data show evidence that extractables are consistently below acceptable and safe levels, elimination of this test can normally be accepted.
- This should be reinvestigated if the container/closure system or formulation changes.

Specific Tests / Criteria : New Drug products

Oral liquids:

g) Alcohol content:

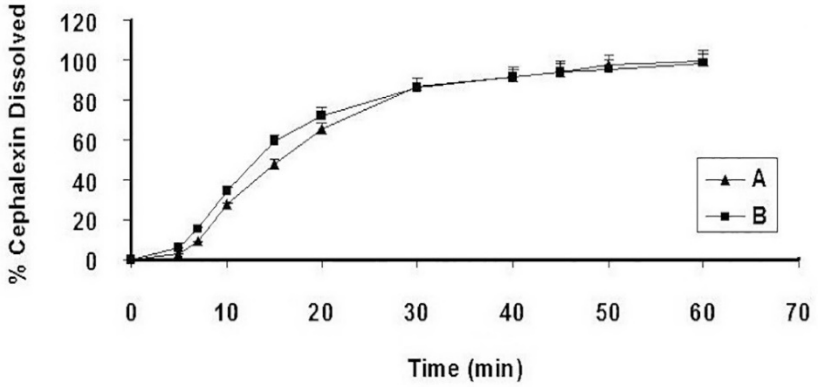
- Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified.
- It may be **assayed or calculated**.

Specific Tests / Criteria : New Drug products

Oral liquids:

h) Dissolution:

- In addition to the attributes recommended immediately above, it may be appropriate (e.g., insoluble drug substance) to include dissolution testing and acceptance criteria for:
  - oral suspensions
  - dry powder products for resuspension.
- The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified.

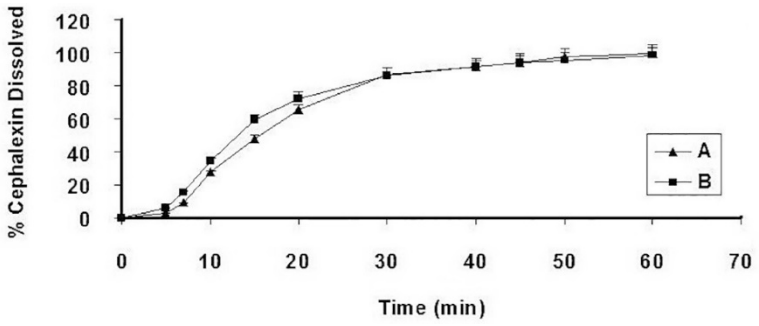


Specific Tests / Criteria : New Drug products

Oral liquids:

h) Dissolution:

- Single-point measurements are normally considered suitable for immediate-release dosage forms.
- Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms.
- Acceptance criteria should take into account the dissolution profiles of the batches that showed acceptable performance in vivo.

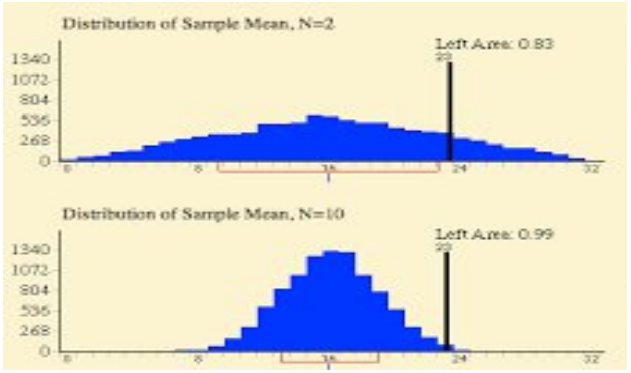


Specific Tests / Criteria : New Drug products

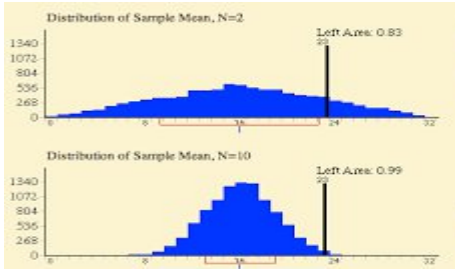
Oral liquids:

i) Particle size distribution:

- Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions.
- performed at release→ in-process test when justified by product development data.



Specific Tests / Criteria : New Drug products

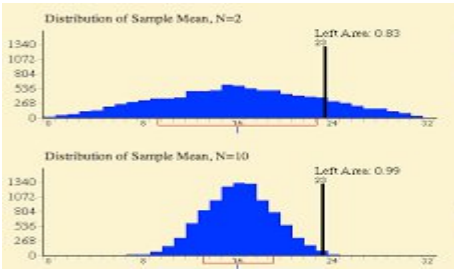


Oral liquids:

i) Particle size distribution:

- If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed.
- Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided.
- Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Specific Tests / Criteria : New Drug products



Oral liquids:

i) Particle size distribution:

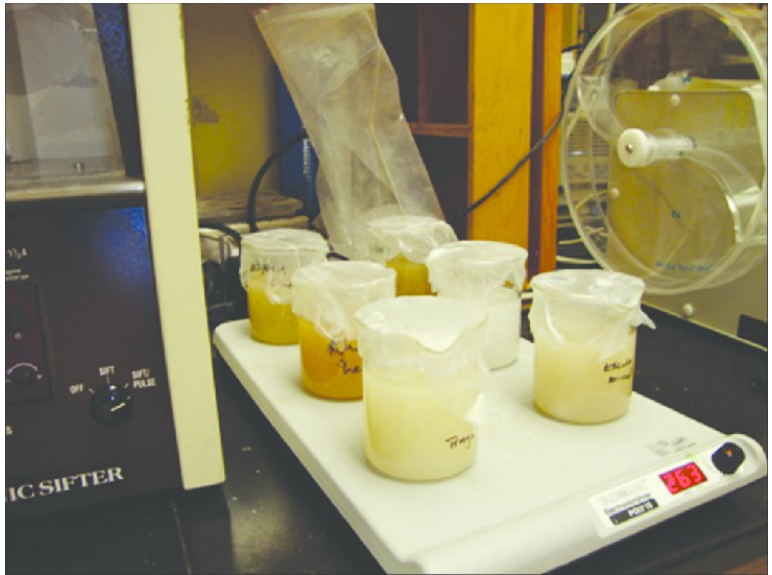
- The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and / or lower particle size limits should be well defined.
- The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

Specific Tests / Criteria : New Drug products

Oral liquids:

j) Redispersibility:

- For oral suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate.
- The procedure (mechanical or manual) should be indicated. Shaking may be an appropriate procedure.



Specific Tests / Criteria : New Drug products

Oral liquids:

k) Rheological properties:

- For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification.

l) Reconstitution time:

- Acceptance criteria for reconstitution time should be provided for dry powder products which require reconstitution.

m) Water content:

- For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate.

Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

a) Uniformity of dosage units

b) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

c) Sterility: All parenteral products should have a test procedure and acceptance criterion for evaluation of sterility. Where data generated during development and validation justify parametric release, this approach may be proposed for terminally sterilized drug products.

d) Endotoxins/Pyrogens: A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification.

Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

e) Particulate matter: Parenteral products should have appropriate acceptance criteria for particulate matter.

This will normally include acceptance criteria for:

1. visible particulates and / or clarity of solution,
2. for sub-visible particulates as appropriate.

f) Water content:

For **non-aqueous** parenterals, and for parenteral products for reconstitution, a test procedure and acceptance criterion for water content should be proposed when appropriate.

Loss on drying (LOD) is generally considered sufficient for parenteral products, if the effect of absorbed moisture vs. water of hydration has been adequately characterized during development.

In certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferred.

Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

***g) Antimicrobial preservative content*:**

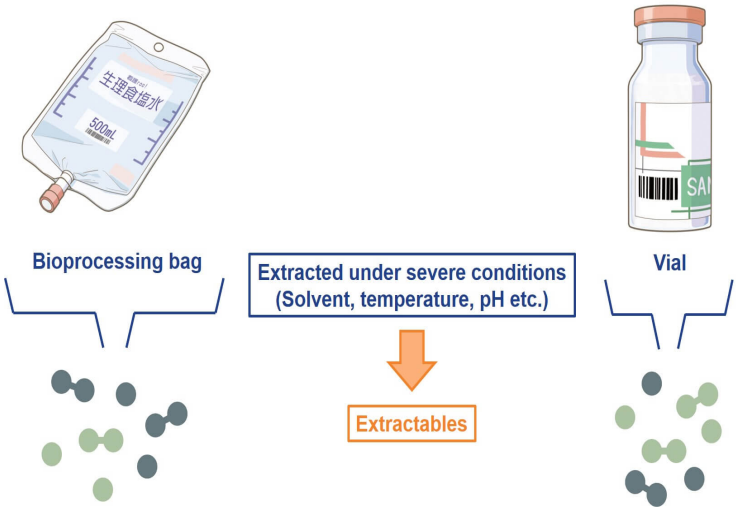
- For parenteral products needing an antimicrobial preservative (e.g. multidose vials).
- The **lowest** specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Specific Tests / Criteria : New Drug products

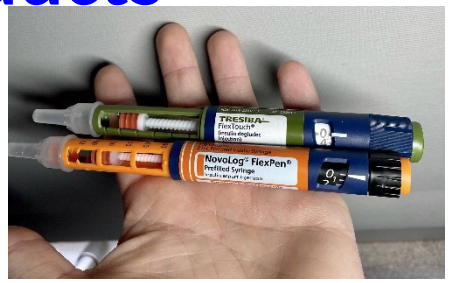
Parenteral Drug Products :

i) Extractables:

- Control of extractables from container/closure systems is considered significantly more important for parenteral products than for oral liquids.
- However, where development and stability data show evidence that extractables are consistently below the levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted.
- This should be **reinvestigated** if the container/closure system or formulation changes.



Specific Tests / Criteria : New Drug products

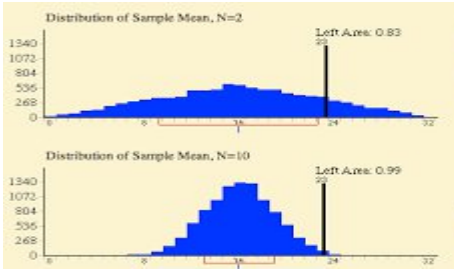


Parenteral Drug Products :

***j) Functionality testing of delivery systems*:**

- Parenteral formulations packaged in pre-filled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system (e.g.inj. volume).
- Under certain circumstances these tests may be performed in-process.
- Data generated during product development may be sufficient to justify skip lot testing or elimination of **some or all a**ttributes from the specification.

Specific Tests / Criteria :
New Drug products



Parenteral Drug Products :

k) Osmolarity: When the tonicity of a product is declared in its labeling, appropriate control of its osmolarity should be performed.

l) Particle size distribution:

Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for injectable suspensions.

Particle size distribution testing may also be proposed in place of dissolution testing, when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided.

m) Redispersibility: similarly to oral liquids

n) Reconstitution time: similarly to oral liquids