Specific tests/criteria
New drug product

Hardness/friability

- It is normally appropriate to perform hardness and/or friability testing as an **in-process control.** Under these circumstances, it is 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.**

Uniformity of dosage units

- This term includes both the mass of the dosage form and 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**; the **acceptance criteria should be included in the specification.**
- When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that tne homogeneity of the product is adequate.

Specific tests/criteria

New drug product

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

Microbial limits

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

The principles discussed here may be applicable to excipients as well as to new drug products.

Skip testing may be an appropriate approach in both cases where permissible.

Acceptance criteria are similar to that of new drug substance.

Guidelines/Oral liquids

Guidelines/Oral liquids

Uniformity of dosage units

- This term includes both the mass of the dosage form and 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. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.
- Tests may be performed in-process; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages.
- 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.
  - The dispensing equipment to be used is normally determined during development.
- For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

Guidelines/Oral liquids

pH

- Acceptance criteria for pH should be provided where applicable and the proposed range justified.

Microbial limits

- It is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, **not to carry a significant risk of microbial contamination or proliferation.**
- Skip testing may be an appropriate approach 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 the total count of aerobic microorganisms, total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa).
- Microbial limits should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience

Guidelines/Oral liquids

Antimicrobial preservative content

Guidelines/Oral liquids

Antimicrobial preservative content

- For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content should be established.
- Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf-life.
- The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.
- Testing for antimicrobial preservative content should normally be performed at release.
- When antimicrobial preservative content testing is performed as an **in-process test**, the acceptance criteria should remain part of the specification.
- Antimicrobial preservative effectiveness should be demonstrated during **development**, during **scaleup**, and throughout the **shelf-life**.

Guidelines/Oral liquids

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 may suffice in lieu of release testing where permitted but the acceptance criteria should remain part of the specification.
- If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.
- **Extractables**
- Generally, where development and stability data show evidence that extractables from the container/closure systems are consistently below 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.
- Where data demonstrate the need, 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, or in glass containers with non-glass closures. **The container/closure components should be listed, and data collected for these components as early in the development process as possible.**

Guidelines/Oral liquids

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.

process as possible.

Guidelines/Oral liquids

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.

Dissolution

- Dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension.
- Dissolution testing should be performed at release.
- This test may be performed as an in-process test when justified by product development data.
- The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated.
- 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 be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo.

Guidelines/Oral liquids

Particle size distribution

- Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions.
- Developmental data should be considered when determining the need for **either a dissolution procedure or a particle size distribution procedure for these formulations.**
- Particle size distribution testing should be performed at release.
- It may be performed as an in-process test when justified by product development data. 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.**
- The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

Guidelines/Oral liquids

Guidelines/Oral liquids

Redispersibility

- For oral suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate.
- Shaking may be an appropriate procedure.
- The procedure (mechanical or manual) should be indicated.
- Time required to achieve resuspension by the indicated procedure should be clearly defined.
- Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

Rheological properties

- For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification.
- The test and acceptance criteria should be stated.
- Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

Guidelines/Oral liquids

Reconstitution time

- Acceptance criteria for reconstitution time should be provided for dry powder products which require reconstitution.
- The choice of diluent should be justified.
- Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification may be proposed.

Water content

- For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate. .
- (1) Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterized during the development of the product.
- In certain cases a more specific procedure (e.g., (2) Karl Fischer titration) may be preferable.

highly specific for water.

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Guidelines/Parenteral Drug Products

(1) Uniformity of dosage units

assay (2) content uniformity + mass or weigh

Guidelines/Parenteral Drug Products

① Uniformity of dosage units

- This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should one or the other but not both and is applicable to powders for reconstitution.
- When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.
- These tests may be performed in-process; the acceptance criteria should be included in the specification.
- This test may be applied to both single-dose and multiple-dose packages.
- For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

② pH

- Acceptance criteria for pH should be provided where applicable and the proposed range justified.

Guidelines/Parenteral Drug Products

- **Sterility** absence microbial contamination
- 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

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.

Particulate matter

- Parenteral products should have appropriate acceptance criteria for particulate matter.
- This will normally include acceptance criteria for visible particulates and / or clarity of solution, as well as for sub-visible particulates as appropriate.

Guidelines/Parenteral Drug Products

Guidelines/Parenteral Drug Products

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 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.

Antimicrobial preservative content

- Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life.
- Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, **in-process** testing may suffice in lieu of release testing where permitted. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.
- Antimicrobial preservative effectiveness should be demonstrated **during development, during scaleup, and throughout the shelf-life**

Guidelines/Parenteral Drug Products

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 and in-process testing may suffice in lieu of release testing.
- When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.
- If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes

Guidelines/Parenteral Drug Products

Extractables

- Control of extractables from container/closure systems is considered significantly more important for parenteral products than for oral liquids.
- When 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. Where data demonstrate the need, acceptance criteria for extractables from the container/closure components are considered appropriate for parenteral products packaged in non-glass systems or in glass containers with elastomeric closures. This testing may be performed at release only, where justified by data obtained during development. The container/closure system components (e.g., rubber stopper, etc.) should be listed, and data collected for these components as early in the development process as possible.

Guidelines/Parenteral Drug Products

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.
  - These may include control of syringeability, pressure, and seal integrity (leakage), and/or parameters such as tip cap removal force, piston release force, piston travel force, and power injector function force.
  - 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 attributes from the specification. Skip lot sampling means that only a Fraction of the submitted lots are inspected.

Osmolarity

- When the tonicity of a product is declared in its labeling, appropriate control of its osmolarity should be performed.
- Data generated during development and validation may be sufficient to justify performance of this procedure as an in-process control, skip lot testing, or direct calculation of this attribute

Guidelines/Parenteral Drug Products

Guidelines/Parenteral Drug Products

Particle size distribution

- Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for injectable suspensions.
- Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.
- Particle size distribution testing should be performed at release. It may be performed as an in-process test when justified by product development data.
- If the product has been demonstrated during development to have consistently rapid drug release characteristics, exclusion of particle size controls from the specification may be proposed.
- 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.
- 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. Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo and the intended use of the product.
- The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account

Guidelines/Parenteral Drug Products

Redispersibility

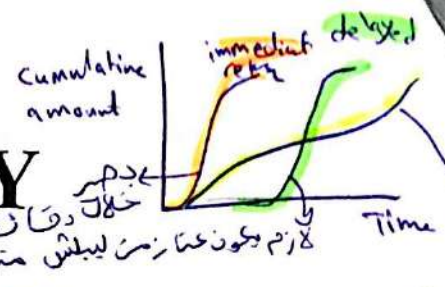
- For injectable suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate.
- Shaking may be an appropriate procedure.
- The procedure (mechanical or manual) should be indicated.
- Time required to achieve resuspension by the indicated procedure should be clearly defined.
- Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

Reconstitution time

- Acceptance criteria for reconstitution time should be provided for all parenteral products which require reconstitution.
- The choice of diluent should be justified.
- Data generated during product development and process validation may be sufficient to justify skip lot testing or elimination of this attribute from the specification for rapidly dissolving products.

GLOSSARY

- **Acceptance criteria**: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.
- **Chiral**: Not superimposable with its mirror image, as applied to molecules, conformations, and macroscopic objects, such as crystals. the term has been extended to samples of substances whose molecules are chiral, even if the macroscopic assembly of such molecules is racemic.
- **Combination product**: A drug product which contains more than one drug substance.
- **Degradation product**: A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of e.g.; light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.



GLOSSARY

- **Delayed Release**: Release of a drug (or drugs) at a time other than immediately following oral administration.
- **Enantiomers**: Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images
- **Extended Release**: Products which are formulated to make the drug available over an extended period after administration

GLOSSARY

- **Highly Water Soluble Drugs**: Drugs with a dose/solubility volume of less than or equal to 250 ml over a pH range of 1.2 to 6.8. (Example: Compound A has as its lowest solubility at 37± 0.5°C, 1.0 mg/ml at pH 6.8, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/ml = 400 ml).
- **Immediate Release**: Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

GLOSSARY

- **Impurity**: (1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance.
- (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product.
- **Identified impurity**: An impurity for which a structural characterization has been achieved.
- **In-process tests**: 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.

GLOSSARY

Modified Release: Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

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.

GLOSSARY

- **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.
- **Polymorphism**: The occurrence of different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.
- **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.

GLOSSARY

- **Racemate**: A composite (solid, liquid, gaseous, or in solution) of equimolar quantities of two enantiomeric species. It is devoid of optical activity.

Rapidly Dissolving Products: An immediate release solid oral drug product is considered rapidly dissolving when not less than 80% of the label amount of the drug substance dissolves within 15 minutes in each of the following media: (1) pH 1.2, (2) pH 4.0, and (3) pH 6.8.

- **Reagent**: A substance, other than a starting material or solvent, which is used in the manufacture of a new drug substance.
- **Solvent**: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.

GLOSSARY

- **Specification**: 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.

GLOSSARY

- **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.
- **Specified impurity**: An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.
- **Unidentified impurity**: An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).
- **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.

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