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⟨2⟩ ORAL DRUG PRODUCTS—PRODUCT QUALITY TESTS

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▲INTRODUCTION

Oral delivery is the most common route of administration for drug products. Through oral delivery, both systemic action and local action in the oral cavity or gastrointestinal tract can be achieved. Oral drug products fall primarily into two categories: solids and liquids. Solid oral dosage forms include but are not limited to capsules, tablets, granules, and powders. Liquid oral dosage forms include but are not limited to solutions, suspensions, and emulsions. The definition and description of these dosage forms and brief information about their compositions and manufacturing processes can be found in *Pharmaceutical Dosage Forms* ⟨1151⟩. [NOTE—All references to chapters above ⟨1000⟩ are for informational purposes only, for use as helpful resources. These chapters are not mandatory unless explicitly called out for application.]

This chapter focuses on product quality tests for oral drug products consisting of a single drug substance or a combination of drug substances. For large or biologic molecules, additional tests may apply. This chapter only applies to drug products for oral administration. Some of the tests indicated in this chapter may be performed as in-process testing or omitted as routine tests based on process validation. However, each batch of the drug product must meet *USP* compendial requirements when sampled and tested once the drug product is released to the market.

This chapter provides a list of consolidated common product quality test requirements for orally administered drug products. This chapter applies, in part or whole, when it is referenced in a drug product monograph (see *General Notices, 3.10 Applicability of Standards*). The quality tests listed can be used as appropriate by manufacturers toward the development of new drug product monographs for submission to *USP*. If a validated performance test procedure is available for the specific drug product, it is identified in a general chapter numbered below ⟨1000⟩. When a validated procedure cannot be recommended, but information is available for a product quality and/or product performance test, it is described in an informational chapter numbered above ⟨1000⟩.

DRUG PRODUCT QUALITY TESTS AND PERFORMANCE TESTS

Monograph tests, analytical procedures, and acceptance criteria for testing oral drug products are divided into two categories: 1) drug product quality tests for general quality attributes, and 2) drug product performance tests for specific quality attributes that may be linked to bioavailability and bioequivalence studies (see *Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution* ⟨1090⟩ and *ICH Guideline M9 Biopharmaceutics Classification System-Based Biowaivers*). Drug product quality tests include identity, strength, purity, quality (physical, chemical, and microbiological), and potency. Drug product performance tests are designed to assess in vitro drug release from dosage forms (e.g., *Dissolution* ⟨711⟩ and *Drug Release* ⟨724⟩).

The above attributes provide a primary understanding of the quality and performance of an oral drug product. As such, these attributes form the basis for a monograph. A compendial drug product should meet all drug product quality tests and drug product performance tests contained in its monograph.

PERFORMANCE TESTS FOR ORAL DRUG PRODUCTS

A performance test is required for all solid oral dosage forms including suspensions. See *Oral Dosage Forms—Performance Tests* ⟨1711⟩, *Disintegration* ⟨701⟩, ⟨711⟩, ⟨724⟩, *The Dissolution Procedure: Development and Validation* ⟨1092⟩, *Capsules—Dissolution Testing and Related Quality Attributes* ⟨1094⟩, and *Disintegration and Dissolution of Dietary Supplements* ⟨2040⟩. The dissolution test may be replaced by a disintegration test with appropriated justification, see ⟨1711⟩. Some dosage forms, such as orally disintegrating tablets and chewable tablets, require both dissolution and disintegration tests, see ⟨1711⟩.

A performance test is not required for oral solutions or solid oral dosage forms intended for reconstitution into a solution.

QUALITY TESTS FOR ORAL DRUG PRODUCTS

Drug product quality tests for oral drug products fall into two categories: 1) universal tests that are applicable to all oral drug products and 2) specific tests that should be considered for testing of specific types of oral products.

Universal Tests for Oral Drug Products

Product quality attributes for oral dosage forms are important to ensure that commercialized products meet minimum quality requirements. Universal tests should be applied to all oral dosage forms and include *Description*, *Identification*, *Strength* (*Assay*), and *Impurities* (organic, inorganic, and residual solvents). *Elemental Impurities—Limits* ⟨232⟩, *Elemental Impurities—Procedures* ⟨233⟩, *Residual Solvents* ⟨467⟩, and, when applicable, *Nitrosamine Impurities* ⟨1469⟩ should also be applied. Extractables and leachables testing is applicable

to liquid dosage forms when packaged in specific container–closure systems and may also be applicable to solid oral forms, particularly when solvents are utilized in the manufacturing process.

DESCRIPTION

Description is general in nature and is not a standard in itself. It communicates the appearance of an article that complies with monograph standards.

IDENTIFICATION

The identification test is defined in *General Notices, 5.40 Identification*. It is included in a monograph as an aid to confirm that the article contains the labeled drug substance. The identification test should provide a positive identification of the drug substance or drug substances in a drug product.

Identification testing should establish the identity of the drug substance(s) in the drug product and should be able to discriminate between the drug substance and the other components in the drug product such as other drug substance(s), impurities, and additives that are likely to be present. Identification tests should be specific for the drug substance, e.g., infrared spectroscopy (see *Spectroscopic Identification Tests ⟨197⟩*). Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. 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 permitted. The results of the identification test must be compared to the results obtained from a similarly prepared, suitable reference standard. Although rare, a specification for polymorphic form could be considered for drug products manufactured from metastable drug substances (*FDA Guidance for Industry ANDAs: Pharmaceutical Solid Polymorphism—Chemistry, Manufacturing, and Controls Information*).

ASSAY

The assay is a specific and stability-indicating test to determine the potency (content) of the drug product. When a nonspecific assay (e.g., titration) is justified, other supporting analytical procedures should ensure that any interfering species can be detected. In general, the *a priori* acceptance of ±10% variation in limits of a quality attribute (e.g., assay) from the target label claim (100%) in most cases is intended to account for manufacturing variability and shelf-life stability and is primarily based on the notion that such variation in a quality attribute is less likely to have any noticeable adverse impact on the desired clinical outcome. Acceptance criteria of 95.0%–105.0% are used with justification (e.g., for drug products with narrow therapeutic index). Activity assays and absolute content assays also are acceptable when justified.

IMPURITIES

Process impurities, synthetic by-products, and other inorganic and organic impurities may be present in the drug substance and in the excipients used in the manufacture of the drug product. These impurities are limited by drug substance and excipient monographs. During product manufacture and over the shelf life of the product, degradation products can form. These degradation products can be a result of degradation of the drug substance or from interactions between the drug substance and excipient(s), among other factors. The procedures and acceptance criteria should specifically limit toxic materials in the drug product. See specific requirements in *General Notices 5.60, Impurities and Foreign Substances*, including considerations of risk-based analysis for ⟨232⟩ and ⟨467⟩. [Note—For additional information, see *Impurities in Drug Substances and Drug Products ⟨1086⟩*, *⟨1469⟩*, the applicable *FDA Guidance for Industry Control of Nitrosamine Impurities in Human Drugs*, and the *ICH Guideline M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.]

Specific Tests for Tablets

In addition to the *Universal Tests for Oral Drug Products* described above, the following specific tests for tablets should be considered, depending upon the nature of the drug substance and formulation.

WATER AND/OR VOLATILE CONTENT

Water and/or volatile content test and the specific method will depend on the nature of the drug product. Special consideration should be given to dosage forms for which water content has been shown to be a potential quality attribute and to products where solvent is used in the manufacture of the drug product.

When moisture or other volatile material may become critical, analysts must determine the amount of unbound volatile solvents or volatile matter of any kind that is driven off by *Loss on Drying ⟨731⟩*, *Water Activity ⟨922⟩*, or another suitable technique. For substances that appear to contain water as the only volatile constituent, the procedure given in *Water Determination ⟨921⟩* may be appropriate. For drug products, analysts should also consult ⟨467⟩.

TABLET FRIABILITY

The tablet friability test is applicable to compressed, uncoated tablets. Friability determines the ability of tablets to withstand mechanical stresses and their resistance to chipping and surface abrasion. [Note—For additional information, see *Tablet Friability ⟨1216⟩*.]

TABLET BREAKING FORCE

Tablet breaking force, commonly known as "tablet hardness", measures the mechanical integrity of tablets, which is the force required to cause them to fail (i.e., break) in a specific plane. [Note—For additional information, see *Tablet Breaking Force ⟨1217⟩*.]

UNIFORMITY OF DOSAGE UNITS

Uniformity of dosage units must be demonstrated by either Content Uniformity or Weight Variation. Content Uniformity is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual contents are sufficiently close to label claim. Weight Variation can be used as an alternative to estimate content uniformity under certain conditions (see *Uniformity of Dosage Units* ⟨905⟩).

Specific Tests for Uncoated Tablets

Uncoated tablets include single-layer tablets that result from a single compression of particles and multilayer tablets that consist of concentric or parallel layers obtained by successive compression of particles of different composition. Uncoated tablets include but are not limited to effervescent tablets, buccal tablets, sublingual tablets, chewable tablets, orally disintegrating tablets, tablets for oral solution, and tablets for oral suspension. *Universal Tests for Oral Drug Products* and *Specific Tests for Tablets* apply for uncoated tablets.

BUCCAL, SUBLINGUAL, AND ORALLY DISINTEGRATING TABLETS

Buccal, sublingual, and orally disintegrating tablets are discussed in *Mucosal Drug Products—Product Quality Tests* ⟨4⟩. See ⟨1151⟩ and the *FDA Guidance for Industry Orally Disintegrating Tablets* for more information on orally disintegrating tablets.

CHEWABLE TABLETS

See *FDA Guidance for Industry Quality Attribute Considerations for Chewable Tablets.*

TABLETS FOR ORAL SOLUTION AND TABLETS FOR ORAL SUSPENSION

Tablets for oral solution and tablets for oral suspension, which can include effervescent tablets, are intended to be dissolved or dispersed in water before administration, respectively resulting in a homogeneous solution or dispersion. The development of a test for reconstitution time should be considered. For tablets reconstituted to form suspensions not intended for immediate use, a quality test should be performed for resuspendability. Development of tests to be performed after reconstitution must be undertaken using the reconstitution process, which will be described on the product label.

Specific Tests for Coated Tablets

Tablets are coated with functional coatings to modify drug release, or nonfunctional coatings to improve stability, to facilitate swallowing, to identify the product or its different strengths, to achieve taste masking, or for esthetical purposes, etc. (see ⟨1151⟩). *Universal Tests for Oral Drug Products* and *Specific Tests for Tablets* apply for coated tablets.

Specific Tests for Capsules

In addition to the *Universal Tests for Oral Drug Products* described above, the specific tests included below for capsules should be considered, depending on the nature of the drug substance and formulation. Modified-release capsules include delayed-release capsules and extended-release capsules.

Product quality tests that are specific to the type of capsule include those for water and/or volatile content (see ⟨731⟩ and ⟨921⟩). One-piece capsules (e.g., soft-shell capsules) typically are used to deliver a solution or suspension. Two-piece capsules (e.g., hard-shell capsules) consist of two telescoping cap-and-body pieces that are typically used to deliver solids such as powders, granules, or small tablets each individually or in combination. See ⟨1094⟩ for additional information.

UNIFORMITY OF DOSAGE UNITS

Uniformity of dosage units must be demonstrated by either Content Uniformity or Weight Variation. Content Uniformity is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual contents are sufficiently close to label claim. Weight Variation can be used as an alternative to estimate content uniformity under certain conditions (see ⟨905⟩).

Specific Tests for Granules

In addition to the *Universal Tests for Oral Drug Products* described above, tests included below should be considered, depending on the nature of the drug substance and formulation.

Granules are solid dosage forms that are composed of agglomerations of smaller particles. Granules include but are not limited to effervescent granules, coated granules, extended-release granules, and delayed-release granules.

Tests that are considered specific to the type of granules include water and/or volatile content (see ⟨731⟩ and ⟨921⟩). For the disintegration test for effervescent granules, refer to ⟨701⟩. On the basis of the nature of the article and scientific criteria, additional tests may apply, including Powder Fineness (see *Powder Fineness* ⟨811⟩) and Content Uniformity (see ⟨905⟩) if granules are packaged in single-unit containers. The development of a test for reconstitution time should be considered. For granules reconstituted to form suspensions not intended for immediate use, a quality test should be performed to test for resuspendability. Development of tests to be performed after reconstitution must be undertaken using the reconstitution process, which will be described on the product label.

Specific Tests for Powders

In addition to the *Universal Tests for Oral Drug Products* described above, the specific tests included below should be considered, depending on the nature of the drug substance and formulation.

Tests that are considered specific to the type of powders include: *Minimum Fill* ⟨755⟩ for products packaged in multiple-dose containers, Content Uniformity (see ⟨905⟩) for products packaged in single-unit containers, and water and/or volatile content (see ⟨731⟩ and ⟨921⟩).

On the basis of the nature of the article and scientific criteria, additional tests may apply, including pH in an aqueous solution, Powder Fineness, Microbial Limits, and others. The development of a test for reconstitution time should be considered. For powders reconstituted to form suspensions not intended for immediate use, a quality test should be performed to test for resuspendability. Development of tests to be performed after reconstitution must be undertaken using the reconstitution process, which will be described on the product label.

Specific Tests for Liquids

The recommended product quality tests for a liquid drug product include the *Universal Tests for Oral Drug Products* described above and the specific tests included below. Most of the quality tests for liquids require the evaluation of single-dose products to estimate the quality attribute. Specific directions to perform the quality tests (including preservative content) for either single-dose or multiple-dose products are provided in the monograph or the general chapter. For example, Weight Variation may be used when adequacy of mix for the active substance(s) and excipients in the blend is well controlled to ensure their uniform distribution, as in solutions.

DELIVERABLE VOLUME

When the liquid formulation is packaged in a multiple-dose container, compliance with *Deliverable Volume* ⟨698⟩ is required.

ALCOHOL DETERMINATION

If the liquid formulation contains a quantity of alcohol, *Alcohol Determination* ⟨611⟩ should be included. The limits may be an absolute concentration, in percentage, or relative to a labeled content.

pH

Liquid oral products typically are aqueous formulations that are susceptible to pH changes from exposure to atmospheric carbon dioxide (CO_2). The uptake of atmospheric carbon dioxide (CO_2) and consequent pH change of oral liquid products is only relevant to aqueous-based products. The pH of an oral liquid formulation can affect flavor and stability. The pH range as outlined in *pH* ⟨791⟩ is indicated in the monograph.

MICROBIAL CONTENT

The microbial load and presence of specific microorganisms in nonsterile preparations may affect the quality of the product and have the potential to adversely affect the health of the patient. The microbial specification needed for a given oral product depends on the dosage form and its use.

Microbial examination of nonsterile drug products is performed according to the methods given in *Tests for Burkholderia Cepacia Complex* ⟨60⟩, *Microbial Enumeration Tests* ⟨61⟩, and *Tests for Specified Microorganisms* ⟨62⟩ unless the formulation itself is demonstrated to have antimicrobial properties. Acceptance criteria for nonsterile pharmaceutical products based on total aerobic microbial count and total combined yeasts and molds count are given in *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩.

ANTIOXIDANT

If an antioxidant is included in the drug product, then appropriate antioxidant release testing should be performed. Shelf-life testing may be unnecessary where justified by development and stability data (*ICH Guideline Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).

EXTRACTABLES AND LEACHABLES

In cases where development studies include extractable assessments and stability data show no significant evidence of extractables or leachables, the elimination of testing for specific leachables may be proposed. During leachable assessment throughout the shelf life, if no significant evidence of extractables or leachables is observed, it may be suggested to eliminate testing for certain leachables. Where data demonstrate the need, tests and acceptance criteria for extractables and leachables from the container–closure system components (e.g., rubber stopper, cap liner, plastic bottle) are considered appropriate for oral solutions packaged in nonglass systems or in glass containers with nonglass closures (see *ICH Guideline Q6A*). Additional information is available in *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩ and its subchapters *Plastic Materials of Construction* ⟨661.1⟩, *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩, *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩, and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩.

ORAL LIQUID DOSAGE FORMS

Types of oral liquid dosage forms include solutions, emulsions, and suspensions.

Specific quality tests for these dosage forms are provided in their respective monographs.

Specific Tests for Miscellaneous Oral Dosage Forms

LYOPHILIZED ORAL PRODUCTS

Water Determination ⟨921⟩, *Method I, Method Ia*: Lyophilized oral products comply with the test. The limits are approved as indicated in the specific monograph. The development of a test for reconstitution time should be considered.

GASTRO-RETENTIVE DOSAGE FORMS

Gastro-retentive dosage forms have specific performance tests (see ⟨1711⟩).▲ (USP 1-Dec-2024)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<2> ORAL DRUG PRODUCTS-PRODUCT QUALITY TESTS	Antonio Hernandez-Cardoso Senior Scientific Liaison	GCDF2020 General Chapters - Dosage Forms 2020

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