⟨2⟩ ORAL DRUG PRODUCTS—PRODUCT QUALITY TESTS

INTRODUCTION

Oral delivery is the most common route of administration for drug products. All oral drug products lead to systemic and/or local action in the oral cavity and/or gastrointestinal tract. Oral drug products fall primarily into two main categories: solids and liquids. Solid oral drug products include but are not restricted to capsules, tablets, granules, and powders. Similarly, liquid oral drug products include but are not restricted to solutions, suspensions, and emulsions. The definitions and descriptions of these dosage forms and brief information about their composition and manufacturing process are found in *Pharmaceutical Dosage Forms* ⟨1151⟩. [NOTE—All references to chapters above ⟨1000⟩ are for informational purposes only, for use as a helpful resource. These chapters are not mandatory unless explicitly called out for application.]

This chapter focuses on the product quality tests that are generally necessary for oral drug products for a single or combination of small molecules of active ingredients. Biologics in solid dosage forms are not considered. In this chapter, the terms "drug substance" and "active ingredient" are used interchangeably. The contents of this chapter do not necessarily apply to drug products that are intended for use other than by oral administration. For example, the chapter does not address oromucosal dosage forms. Some of the tests indicated in this chapter may be performed on an in-process basis or omitted as routine tests based on process validation. However, the product must meet USP compendial requirements when sampled and tested, once the product is on the market.

This chapter provides lists of consolidated common product quality test requirements in a concise and coherent fashion. This chapter applies, in part or whole, when referenced in a drug product monograph (see *General Notices, 3.10 Applicability of Standards*). This chapter includes the quality tests for the specific route of administration. 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 below ⟨1000⟩. In cases where a validated procedure cannot be recommended, but if the information is available for a product quality and/or product performance test, it is described in an informational chapter 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) those that assess general product quality attributes, and 2) those that assess product performance, which is a specific quality attribute typically linked to bioavailability and bioequivalence studies (see *Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution* ⟨1090⟩). Drug product quality tests are intended to assess attributes such as identification, strength (assay), impurities , dose content uniformity, pH, minimum fill, alcohol content, volatile content, and microbial content. Drug product performance tests are designed to assess in vitro drug release from dosage forms (e.g., *Dissolution* ⟨711⟩ and *Drug Release* ⟨724⟩). For liquid oral drug products in solution, performance is considered optimal, and a monograph performance test is not included.

Each of these attributes is important for a primary understanding of the quality and performance of a drug product. Thus, they form the basis for the monograph. A compendial product should meet all drug product quality tests and drug product performance tests contained in its monograph.

[NOTE—Dissolution tests, specifically dissolution profile similarity between higher strengths and lower strengths of a given manufacturer's product and dissolution profile similarity between the generic product and the reference product, are used for granting biowaivers. See ⟨1090⟩.]

Change to read:

PRODUCT 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 should be included in the monograph, and 2) specific tests that should be considered for inclusion for 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).

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 by providing a positive identification of the drug substance or substances in a drug product.

One method of confirming the identity is to compare the retention time of the sample with that obtained for the standard injections in a chromatographic assay procedure. Other methods often used to orthogonally confirm the identity of the active ingredient are: *Thin-Layer Chromatographic Identification Test* ⟨201⟩, *Spectroscopic Identification Tests* ⟨197⟩, *Nuclear Magnetic Resonance Spectroscopy* ⟨761⟩, *Near-Infrared Spectroscopy—Theory and Practice* ⟨1856⟩, and ▲*Raman Spectroscopy—Theory and Practice* ⟨1858⟩▲ (CN 1-Aug-2020), among others. The analytical procedure must be able to distinguish the active ingredient from all excipients that are present or from potential degradation products likely to be present. Care must also be taken to ensure that the chromatographic system separates the article from other closely related drug substances, impurities, and additives. Infrared and ultraviolet absorption also can be used for identification (see ⟨197⟩), if the procedure has been demonstrated to be selective for the drug substance via an appropriate validation or verification study. The results of the identification test must be compared to the results obtained from a similarly prepared, suitable Reference Standard.

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 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. See specific requirements in the *General Notices 5.60, Impurities and Foreign Substances*. [NOTE—For additional information, see *Impurities in Drug Substances and Drug Products* ⟨1086⟩.]

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.

VOLATILE CONTENT

The test and the specific method depend on the nature of the article. 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 the presence of 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⟩ or another suitable technique (e.g., water activity). 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 also should consult *Residual Solvents* ⟨467⟩.

DISINTEGRATION

Disintegration is an essential attribute of oral solids, except for those intended to be chewed before being swallowed and for delayed- or extended-release products. This test measures the time it takes for the dosage unit to disintegrate in an aqueous medium and is described in detail in *Disintegration* ⟨701⟩. Certain dosage forms (e.g., effervescent tablets and others) may require special procedures and identity tests for bicarbonate when dissolved in water. The disintegration test for some of the dosage forms in this chapter is included for completeness. For detailed procedures, refer to ⟨701⟩. The disintegration test, if included, is used only as a quality control test and not as a product performance test and should conform with the specifications in the monograph. Only when disintegration has been correlated with dissolution of a dosage form can a disintegration test be used as a product performance test [International Council for Harmonisation (ICH) Guidance Q6A, available at www.ich.org]. In all other instances, a dissolution test should be considered as a product performance test.

TABLET FRIABILITY

The test procedure is applicable to most 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 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. The excipients used generally are not specifically intended to modify the release of the active substance in the digestive fluids. 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. For uncoated tablets, disintegration should be tested as directed in ⟨701⟩.

BUCCAL, SUBLINGUAL, AND ORALLY DISINTEGRATING TABLETS

These dosage forms are discussed in *Mucosal Drug Products—Product Quality Tests* ⟨4⟩. They are listed here for informational purposes and completeness.

CHEWABLE TABLETS

Chewable tablets (intact) should undergo dissolution and disintegration testing, as a product performance test (if cited in the monograph), because they might be swallowed without proper chewing by a patient. In general, the dissolution and disintegration test conditions for chewable tablets should be the same as for nonchewable tablets of the same active ingredient or moiety.

TABLETS FOR ORAL SOLUTION AND TABLETS FOR ORAL SUSPENSION

These are tablets intended to be dissolved or dispersed in water before administration, giving a homogeneous solution or dispersion. They are listed here for informational purposes and completeness.

Specific Tests for Coated Tablets

Coated tablets are tablets covered with one or more layers of mixtures of various substances such as natural or synthetic resins, gums, gelatin, inactive and insoluble excipients, sugars, plasticizers, polyols, waxes, coloring matter authorized by the competent authority, and sometimes flavoring substances and active substances. Tablets coated by sugar or film include but are not limited to: plain coated tablets, extended-release tablets, and delayed-release tablets. A disintegration test, when applicable, should be performed as directed in ⟨701⟩.

There are no additional specific quality tests for extended-release tablets and delayed-release tablets. Universal quality tests should be applied to these products.

Specific Tests for Capsules

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. Modified release capsules include delayed-release capsules and extended-release capsules.

Product quality tests that are considered specific to the type of capsule include those for volatile content (see ⟨731⟩ and ⟨921⟩). One-piece capsules typically are used to deliver a drug substance as a solution or suspension. Two-piece capsules consist of two telescoping cap-and-body pieces that are used to deliver solid material as powder, granules, or small tablets.

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⟩).

DISINTEGRATION

For capsules, proceed as directed in ⟨701⟩, if a disintegration test is required. Disintegration for modified release capsules may require special procedures.

There are no additional specific quality tests for modified release capsules. Universal quality tests should be applied to these products.

Specific Tests for Granules

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.

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 volatile content (see ⟨731⟩ and ⟨921⟩). For disintegration 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 and content uniformity (see ⟨905⟩) if granules are packaged in single-unit containers.

Specific Tests for Powders

Oral powders should indicate: "For Oral Use Only". 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 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.

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 presence of certain microorganisms in nonsterile preparations may have the potential to reduce or even inactivate the therapeutic activity of the product and has a potential to adversely affect the health of the patient. Some liquid oral products can be subject to extreme microbiological control, and others require none. The needed microbial specification for a given liquid oral product depends on its formulation and use and is indicated in the monograph.

[NOTE—For additional information, see *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩.]

ANTIOXIDANT

Release testing should be performed. Shelf-life testing may be unnecessary where justified by development and stability data (ICH Guidance Q6A).

EXTRACTABLES

Where development and stability data show no significant evidence of extractables, elimination of this test may be proposed. Where data demonstrate the need and acceptance criteria for oral solutions—rubber stopper, cap liner, plastic bottle—data should be collected as early in the development process as possible (ICH Guidance Q6A).

TYPES OF LIQUID DOSAGE FORMS

Specific quality tests for these dosage forms are provided in their respective monographs.
Solutions, powders, and granules for solution: Tests of "for Solution" formulations are conducted on a well-mixed solution of the drug product constituted as described in the labeling.
Emulsions, suspensions, and powders and granules for suspension: Tests of "for Suspension" formulations are conducted on a well-mixed suspension of the drug product constituted as described in the labeling. Product quality tests for suspensions should include a test of suspendability.
Powders and granules for solutions: After dissolution or suspension, they comply with monograph requirements for the final dosage form. Volatile content (see ⟨731⟩ and ⟨921⟩) may be an additional quality test for powders and granules for reconstitution.

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.