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BRIEFING

⟨**1664.5**⟩ **Oral Dosage Forms.** The General Chapters—Dosage Forms Expert Committee is proposing to add this new chapter as a companion to Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems ⟨1664⟩. This new chapter addresses specific considerations for leachables in oral dosage forms (ODFs), including liquids (solutions, suspensions, emulsions, elixirs, and syrups), semisolids and pastes, and solids (tablets, capsules, powders, granules, and premixes). The chapter considers leachables from two sources: manufacturing systems used to produce the dosage form and container closure systems used to package the dosage form throughout its shelf life. Note that the following discussion is primarily devoted to organic leachables. For consideration of inorganic (i.e., elemental) leachables, see ⟨1664⟩.

(GCDF: R. Kaja)
Case ID—SUB-2257

Add the following:

▲⟨1664.5⟩ ORAL DOSAGE FORMS

1. INTRODUCTION

This chapter contains leachables testing guidelines for oral dosage forms, specifically addressing liquid, semisolid, and solid formulations. The chapter considers leachables from two sources: manufacturing systems used to produce the dosage form and container closure systems used to package the dosage form over its shelf life.

Oral dosage forms (ODFs) are pharmaceutical formulations that are taken by mouth, swallowed, and directed to the gastrointestinal tract, enabling the systematic delivery of the active pharmaceutical ingredient to the body. Oral dosage forms include liquids (LODFs; solutions, suspensions, emulsions, elixirs, and syrups), semisolids and pastes (SSODFs), and solids (SODFs; tablets, capsules, powders, granules, and premixes) as defined and described in *Pharmaceutical Dosage Forms* ⟨1151⟩. ODFs can be further categorized based on their composition, as described below.

LODF

- An LODF is a homogeneous liquid preparation containing one or more active ingredients in a suitable liquid base (solution, emulsion, or suspension). Oral liquids may contain other substances such as suitable solubilizing, emulsifying, stabilizing (e.g., antioxidants and preservatives), suspending, and thickening agents; antimicrobial substances for preservation; pH buffers; and suitable sweetening agents, flavoring agents, and permitted coloring agents. In addition to the excipients above for solutions, *suspensions* may include surfactants and thickening agents.
- *Emulsions* include an emulsifying agent, which prevents coalescence of the dispersed droplets, buffers, antioxidants, and preservatives. Emulsions for oral administration are usually oil (such as castor oil or liquid paraffin as the active ingredient) in water.
- A *syrup* is a concentrated aqueous solution of sugar or a sugar substitute with or without flavoring agents and a water-soluble drug. Sucrose is the most frequently used sugar, and syrups usually contain 60%–80% sugar. Syrups may also contain cosolvents, solubilizing agents, thickeners, or stabilizers.

SSODF

- An SSODF is typically a two-component semisolid in which a drug is dispersed as a powder in an aqueous or fatty base. The vehicle containing the drug may be water; a polyhydroxy liquid such as glycerin, propylene glycol, or polyethylene glycol; a vegetable oil; or a mineral oil. Other formulation excipients include thickening agents, cosolvents, adsorbents, humectants, and preservatives.

SODF

- An SODF can include one or more active pharmaceutical ingredients, fillers, binders, disintegrants, lubricants, coatings, preservatives and/or stabilizers, taste enhancers, and other excipients, as appropriate.

2. PACKAGING FOR ORAL DOSAGE FORMS

2.1 LODF

The packaging systems for liquid oral drugs mainly include:

- Multidose containers—Bottles are typically used, and depending on the specific requirements of the medicine, these can be made of glass or plastic. The packages can be strengthened by specific additives that increase the barrier properties against moisture, oxygen, or light.
- Single-dose containers—Vials or small bottles are typically used, suitable for administering a single dose of the drug.

These dosage forms are generally marketed in multiple-unit bottles or in unit-dose or single-use pouches or cups. The dosage form may be used as-is or admixed first with a compatible diluent or dispersant. A bottle is usually glass or plastic, often with a screw cap with a liner, and possibly with a tamper-resistant seal or an over cap that is welded to the bottle. The same cap liners and inner seals are sometimes used with solid oral dosage forms. Bottles may use an overwrap, which is usually a laminated material. A single-dose cup may be metal or plastic with a heat-sealed lid made of a laminated material. Bottles may be labeled or printed to provide identifying, utilization, and dosing information.

2.2 SSODF

Semi-solid oral dosage forms are typically packaged in flexible tubes or pouches that allow for the SSODF to be adequately administered by "squeezing" the tube to dispense the dosage form. These tubes or pouches are comprised of multilaminate films that are bound together by tie layers or adhesives. The films are composed of various materials that include a relatively low-interacting product contact layer, a gas/moisture barrier layer, and a protective, printable outer layer designed to provide puncture and/or tear resistance to the flexible tubes and pouches. Metal can be used as the material of construction for tubes when barrier properties greater than plastic are required. This would be the case when the drug product formulation contains volatile ingredients, such as various alcohols. The shoulders of these plastic-based multilaminate tubes are often constructed from a single plastic, such as high-density polyethylene or polypropylene, and do not have the same barrier properties as the laminate tube. The tube or pouch can be heat-sealed or folded and crimped using a sealant or adhesive.

Closures for tubes are typically made of polypropylene or polyethylene screw caps having various designs and configurations that can facilitate the administration of the drug product and determine if the tube is stored upright or on its side.

2.3 SODF

Bottles and blister packs are the two most prevalent tablet packaging formats. A typical bottle system includes the plastic (usually high-density polyethylene, HDPE) bottle with a screw-on or snap-off closure that can include a cap, a liner, and an inner seal. Relevant information about the drug product is captured by a label affixed to, or text printed on, the outside of the bottle or blister.

Generally, high-density polyethylene and polypropylene bottles are used for tablets. If transparency is required, polyethylene terephthalate (PET) bottles can be used. If SODFs need higher barrier properties and/or protection from light, brown PET bottles are used. Bottles made of polyethylene naphthalate (PEN) offer superior barrier properties. Desiccants, fillers, and other absorbent materials may be placed in the bottle along with the SODF.

A blister package usually consists of a lidding material and a cavity or pocket made from a formable film. The lidding material is usually a laminate (e.g., aluminum foil–PVC, polyamide–aluminum–PVC) which includes a barrier layer (e.g., aluminum foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side. The sealing side contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. Cavities are pre-formed using thermoform or cold press techniques and provide structural protection for the dosage form.

With regard to materials of construction, polyvinyl chloride (PVC) is commonly used for making blister cavities, given its barrier properties, ease of shaping, and cost. However, PVC can interact with an SODF's ingredients, adversely affecting their stability and effectiveness. Thus, another material, such as polyvinylidene chloride (PVDC), can be added to the surface of PVC to provide a less reactive blister coating. Other materials that can be used in blister cavities include PET, cyclic olefin polymers (COP), and polychlorotrifluoroethylene (PCTFE). Although polystyrene (PS) is widely used in medical blister packaging as the backing board, it is marginally effective as a barrier. Thus, aluminum foil, with its excellent barrier properties, is a common material for making backing boards. Materials used in lidding include PET and paper.

Solid oral dosage forms generally need to be protected from the potential adverse effects of water vapor. Protection from light and reactive gases may also be needed.

Packaging for SODFs may be labeled or printed to provide identifying, utilization, and dosing information.

3. MANUFACTURING SYSTEMS FOR ORAL DOSAGE FORMS

3.1 LODF

Manufacturing systems for LODFs include the following essential equipment:

- Mixing tanks—Used to mix the active pharmaceutical ingredients (APIs) with excipients and the vehicle.
- Filtration systems—Used to remove impurities and ensure product clarity and purity.
- Filling and capping machines—Used to fill bottles or containers with the liquid drug product, cap the filled bottles, and, as appropriate, apply labeling and any secondary packaging. Note that filling lines may contain plastic, silicone, or elastomeric components.

Other than the exception noted above, equipment used in these processes is multiple-use and metallic, predominantly stainless steel.

3.2 SSODF

SSODFs use manufacturing equipment similar to that used for LODFs. The main difference is that processing temperatures for SSODFs are often higher than those for LODFs or SODFs. These higher temperatures can increase the risk of leachables originating from processing components made of polymeric materials.

3.3 SODF

SODFs typically consist of a dry powder formulation that includes the drug substance or API, various excipients, intermediates, and fillers. They are manufactured via processes that involve either solids or a combination of liquids and solids. These processes include:

- Wet granulation
- Dry granulation
- Direct compression
- Particle coating

Almost without exception, equipment used in these processes is multiple-use and metallic, predominantly stainless steel.

4. REGULATORY GUIDELINES FOR ORAL DOSAGE FORMS

4.1 Packaging

Requirements for extractables and leachables testing of SODFs are found in the FDA's *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics* (*1*).

For SODFs, the FDA notes that the risk of interaction between packaging components and a solid oral dosage form is generally recognized to be small, and that for solid oral dosage forms, a reference to the relevant indirect food additive regulation for each material of construction is typically considered sufficient evidence of safety.

For LODFs, the FDA notes that container closure systems for LODFs typically consist of glass or plastic components.

For glass components, data showing that a component meets the requirements of *Containers—Glass* ⟨660⟩ are accepted as sufficient evidence of safety and compatibility.

For plastic components (LDPE specifically), the FDA notes that "data from USP Containers tests are typically considered sufficient evidence of compatibility". Currently, these tests are found in *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩ and *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩.

Furthermore, the FDA notes that a patient's exposure to leachables from plastic packaging components (e.g., HDPE, LDPE, PP, laminates) into a liquid-based oral dosage form is comparable to a patient's exposure to the same substances from food packaging. Based on this assumption, an appropriate reference to the indirect food additive regulations (21 CFR Parts 174–186) is typically considered sufficient to establish the safety of the material of construction, provided any limitations specified in the regulations are taken into consideration. This assumption is considered valid for liquid-based oral dosage forms that the patient will take only for a relatively short time (acute dosing regimen) and if the drug product has the same or lower "extracting power" than the food or beverage cited to the relevant food additive regulation.

For liquid-based oral drug products that the patient will continue to take for an extended period [i.e., months or years (chronic drug regimen)], the FDA guidance notes that a material of construction that meets the requirements for indirect food additives will be considered safe—on that basis alone—only if the patient's exposure to extractables is expected to be no greater than the exposure through foods, or if the length of exposure is supported by toxicological information. For example, if the dosage form is aqueous-based and contains little or no cosolvent (or other substance, including the active drug substance, liable to cause greater extraction of substances from plastic packaging components than would be extracted by water), meeting the requirements of the indirect food additive regulations will usually satisfy the issue of safety.

Lastly, if the dosage form contains cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), the FDA notes that additional information on extractables—and potentially leachables—may be needed to address safety issues.

4.2 Manufacturing Systems

In general, the active ingredient in an ODF is a nonbiologic. Biologic drugs are typically delivered parenterally, rather than orally, because they degrade in the gastrointestinal space and do not easily permeate across biological barriers. The physiological role of the gastrointestinal tract presents multiple barriers that limit the systemic absorption of complex macromolecules after ingestion.

Thus, orally administered drug products typically fit the description of "traditional" or "small molecule" products described in *Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products* ⟨665⟩. As noted in this chapter, such products are "well-characterized … [and] result from manufacturing processes that include multiple, highly effective purification processes", and thus do not require characterization with respect to manufacturing-related extractables and leachables. Furthermore, since the manufacturing systems used for ODFs are typically constructed from metallic components, the issue of organic extractables or leachables is moot. Moreover, because ODFs are considered a low-risk dosage form for packaging systems, they trigger one of the risk mitigation factors established in *Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products* ⟨1665⟩, and are likewise considered low-risk from the perspective of manufacturing systems. Finally, for SODFs specifically, the fact that the "process stream" is a solid means that no extractables or leachables testing is required because the ability of a solid process stream to leach substances from manufacturing components is low.

5. CHEMICAL ASSESSMENT REQUIREMENTS FOR AN ODF

5.1 General Discussion

ODFs are generally categorized as a low-risk dosage form due to the low safety risk related to the route of administration and a low probability of packaging component interaction with the formulation (see *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩, *Table 1*).

Patient exposure to leachables in ODFs is similar to patient exposure to leachables in food because the route of administration is the same. Importantly, however, patient exposure to leachables in ODFs is much less than patient exposure to leachables in foods as the dose (i.e., the amount of an oral medication taken compared with the amount of food consumed) is lower.

These observations are the basis of the previously noted regulatory guidelines, which essentially state that if an item complies with the relevant compendial requirements and meets the relevant food contact regulations, then the item is safe for use in packaging or manufacturing systems for an ODF.

5.2 Packaging

Consistent with existing regulatory guidelines and current regulatory practice, packaging systems used for ODFs must be well-characterized; that is,

- The packaging system itself, or all of its relevant materials of construction, complies with the relevant compendial monographs, and
- The packaging system itself, or all of its relevant materials of construction, complies with the relevant food contact safety regulations (e.g., 21 CFR Parts 174–186), and compliance is adequately justified [e.g., proposed use is consistent with regulations for food contact use, the leaching propensity of the oral dosage form is similar to or less than the extraction solvent(s) listed in a referenced regulation, and all specified testing results for the packaging system or material meet the specified acceptance criteria].

For SODFs, no additional requirements (e.g., extractables and leachables testing) must be met. If fillers, desiccants, or other absorbent materials are placed in the bottle along with the SODF, they must also be well-characterized.

For aqueous LODFs that do not contain surfactants, solubilizing agents, or cosolvents, no additional requirements (e.g., extractables and leachables testing) must be met.

For aqueous LODFs that contain leaching-enhancing agents such as surfactants, cosolvents, or solubilizers, no additional requirements (e.g., extractables and leachables testing) must be met if the leaching propensity of the LODF is adequately addressed by the relevant cited CFR indirect food regulations. If the leaching propensity of the LODF is not adequately addressed by these regulations, then both extractables and leachables testing are required.

Chapters *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩ and ⟨1664⟩ should be consulted to facilitate the design and implementation of any necessary extractables and leachables studies.

When considering extractables and/or leachables testing, consultation with the relevant regulatory agency and/or health authority prior to implementation of such testing may be warranted.

5.3 Manufacturing Systems

Metallic components used to manufacture ODFs do not require qualification for organic substances, as metallic components are not sources of organic extractables and leachables. The risk that metallic components could leach elemental impurities into ODFs must be assessed. Assessments that conclude that there is a high risk of leaching of elements must be followed by appropriate extractables or leachables testing. If extractables testing does not reveal extracted elements in excess of the appropriate control threshold [e.g., 30% of the element's permissible daily exposure (PDE)], then testing manufactured drug products for manufacturing-related leached elements is not required.

Plastic components used to manufacture ODFs, or their relevant materials of construction, must be well-characterized:

- The manufacturing system itself, or all of its relevant materials of construction, complies with the relevant compendial monographs, and
- The manufacturing system itself, or all of its relevant materials of construction, complies with the relevant food contact safety regulations (e.g., 21 CFR Parts 174–186) and compliance is adequately justified [e.g., proposed use is consistent with regulations for food contact use, the leaching propensity of the oral dosage form is similar to or less than the extraction solvent(s) listed in a referenced regulation, and all specified testing results for the manufacturing system or material meet the specified acceptance criteria].

For SODFs, no additional requirements (e.g., extractables and leachables testing) must be met for plastic manufacturing components.

For LODFs, the risk that plastic manufacturing components could leach organic impurities into LODFs must be assessed. Assessments that conclude that there is a high risk of leaching of organic impurities must be followed by appropriate extractables or leachables testing. Based on the outcome of extraction studies, leachables studies may also be required on a case-by-case basis. For example, if extractables testing does not reveal extracted organic impurities in excess of the appropriate control threshold [e.g., 30% of the impurity's permissible daily exposure (PDE)], then leachables testing is not required. However, the semi-quantitative method used in the extraction study must be qualified, consistent with ⟨1663⟩ and ⟨1664⟩.

Chapters ⟨665⟩ and ⟨1665⟩ should be consulted to facilitate the design and implementation of any necessary extractables and leachables studies.

5.4 Auxiliary Dispensing Devices

LODFs may be packaged with dosage dispensing devices intended to facilitate proper dispensing of the product by the patient, parent, or caregiver. In general, contact between the dosage dispensing device and the LODF is transient and thus the possibility that substances would be leached from the dosage dispensing device by the dispensed LODF in sufficient quantities to adversely affect patient safety is low.

Auxiliary dispensing devices must be constructed from materials that comply with the relevant compendia. Proper extraction studies for auxiliary dispensing devices may be required on a case-by-case basis. However, when the device's materials of construction are well-characterized (meaning that they also comply with the relevant food contact safety regulations), extractables studies are not required. When considering the elimination of extractables testing, consultation with the relevant regulatory agency and/or health authority prior to implementation may be warranted. Leachables testing is only required in the expectedly rare circumstance that extractables testing reveals one or more extractables that present a potential patient safety risk and is limited to a targeted assessment of the specific extractables that may pose a potential patient safety risk.

5.5 Nitrosamines

Certain packaging systems used with ODFs are potential sources of nitrosamines (e.g., nitrosamines can be present in blister packaging for

ODFs due to the use of nitrocellulose in the lidding foil). Thus, packaging systems for ODFs should be risk-assessed as potential sources of nitrosamines. If it can be or has been established that the packaging system is likely not a potential source of nitrosamines (low-risk), then further consideration of nitrosamines being present in the drug product is not necessary. However, if a low risk of nitrosamines leaching from packaging cannot be established with existing information, then nitrosamine testing of controlled extracts or packaged ODFs is recommended.

REFERENCES

1. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; Center for Biologics Evaluation and Research. *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation*. May 1999. *www.fda.gov/media/70788/download*.▲ (USP 1-Dec-2026)

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

Topic/Question	Contact	Expert Committee
<1664.5> ASSESSMENT OF LEACHABLES IN ORAL DRUG PRODUCTS	Ravikiran Kaja Senior Principal Scientist	GCDF2025 Dosage Forms
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