A change in formulation is considered a change in the specifications for the packaging component. This change in the formulation of a packaging component by its manufacturer should be reported to the firm that purchases that component and to any appropriate DMF. The firm that purchases the component should, in turn, report the change to its application as required under 21 CFR 314.70(a) or 601.12. Manufacturers who supply a raw material or an intermediate packaging component should inform their customers of any intended changes to formulations or manufacturing procedures and update the DMF in advance of implementing such a change. Changes which seem innocuous may have unintended consequences on the dosage form marketed in the affected packaging system.

The use of stability studies for monitoring the consistency of a container closure system in terms of compatibility with the dosage form and the degree of protection provided to the dosage form is accepted. Currently there is no general policy concerning the monitoring of a packaging system and components with regard to safety. One exception involves inhalation drug products for which batch-to-batch monitoring of the extraction profile for the polymeric and elastomeric components is routine.

3. Associated Components

*Associated components* are packaging components that are typically intended to deliver the dosage form to the patient but are not stored in contact with the dosage form for its entire shelf life. These components are packaged separately in the market package and are either attached to the container upon opening or used only when a dose is to be administered. Measuring spoons, dosing cups, measuring syringes, and vaginal delivery tubes are examples of associated components that typically contact the dosage form only during administration. A hand pump or dropper combined into a closure are examples of an associated component that would contact the dosage form from the time the packaging system is opened until the dosing regimen is completed.

The complete and assembled component and its parts should meet suitability criteria appropriate for the drug product and the actual use of the component (see sections III.B.1 and III.B.2). Safety and functionality are the most common factors to be established for suitability. The length of time that the associated component and the dosage form are in direct contact should also be taken into consideration when assessing the suitability of an associated component.

4. Secondary Packaging Components

Unlike primary and associated packaging components, *secondary packaging components* are not intended to make contact with the dosage form. Examples are cartons, which are generally constructed of paper or plastic, and overwraps, which may be fabricated from a single layer of plastic or from a laminate made of metal foil, plastic, and/or paper.

A secondary packaging component generally serves one or more of the following additional functions:

a. Provides protection from excessive transmission of moisture or solvents into or out of the packaging system

b. Provides protection from excessive transmission of reactive gases (atmospheric oxygen, inert headspace filler gas, or other organic vapors) into or out of the packaging system

c. Provides light protection for the packaging system

d. Provides protection for a packaging system that is flexible or needs extra protection from rough handling

e. Provides an additional measure of microbiological protection (i.e., by maintaining sterility or by protecting the packaging system from microbial intrusion)

When information on a container closure system is submitted in an application, the emphasis would normally be on the primary packaging components. For a secondary packaging component, a brief description will usually suffice unless the component is intended to provide some additional measure of protection to the drug product. In this case, more complete information should be provided, along with data showing that the secondary packaging component actually provides the additional protection (see sections III.B.1 and III.B.2).

Because secondary packaging components are not intended to make contact with the dosage form, there is usually less concern regarding the materials from which they are constructed. However, if the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component, or from a volatile substance present in the secondary packaging component. (For example, a solution packaged in a LDPE container was found to be contaminated by a volatile constituent of the secondary packaging components that enclosed it.). In such a case, the secondary packaging component should be considered a potential source of contamination and the safety of its materials of construction should be taken into consideration.

## C. Information That Should Be Submitted in Support of an Original Application for Any Drug Product[15]

Additional discussion and information regarding the CMC information to be provided in an application (NDA, ANDA, or BLA) can be found in the guidances and guidelines listed in Attachment E.

1. Description

A general description of the entire container closure system should be provided in the CMC section of the application. In addition, the following information should be provided by the applicant for each individual component of the packaging system:

a. Identification by product name, product code (if available), the name and address of the manufacturer, and a physical description of the packaging component (e.g., type, size, shape, and color)

b. Identification of the materials of construction (i.e., plastics, paper, metal, glass, elastomers, coatings, adhesives, and other such materials) should be identified by a specific product designation (code name and/or code number) and the source (name of the manufacturer).[16] Alternate materials of construction should also be indicated. Postconsumer recycled plastic should not be used in the manufacture of a primary packaging component. If used for a secondary or associated component, then the safety and compatibility of the material for its intended use should be addressed appropriately.

c. Description of any operations or preparations that are performed on a packaging component by the applicant (such as washing, coating, sterilization, or depyrogenation)[17]

2. Information About Suitability

---

[15] See Table 3 for additional information. This section applies to primary packaging components and to those associated and secondary packaging components that provide protection to the drug product or for which there may be a safety concern (see section III.B).

[16] Where possible, this information should be included in the application. Alternatively, it may be provided in a drug master file (see section V) and a letter of authorization (LOA) to the DMF submitted in the application. The LOA permits the Agency to review the information in support of a particular application.

[17] For further information see the FDA guidance for industry *Submission of Documentation for the Sterilization Process Validation in Applications of Human and Veterinary Drug Products* (November 1994).

a. To establish safety and to ensure consistency, the complete chemical composition should be provided for every material used in the manufacture of a packaging component.

b. Test results from appropriate qualification and characterization tests should be provided. Adequate information regarding the tests, methods, acceptance criteria, reference standards, and validation information should be provided.

To address protection, use of USP tests (see Attachment A) for light transmission, moisture permeation, microbial limits, and sterility are generally considered sufficient. Testing for properties other than those described in USP (e.g., gas transmission, solvent leakage container integrity) may also be necessary.

To address safety and compatibility, the results of extraction/toxicological evaluation studies should be provided for drug products that are likely to interact with the packaging components and introduce extracted substances into the patient (see Table 1). For drug products less likely to interact, other tests (e.g., USP Biological Reactivity Test) or information (e.g., appropriate reference to the indirect food additive regulations at 21 CFR 174-186) could be used to address the issue of safety and compatibility (see Table 2). For example, an appropriate reference to an indirect food additive regulation is generally sufficient for a solid oral dosage form product.

To address performance, the results of USP and non-USP functionality tests are considered sufficient if the test and acceptance criteria are appropriate for the intended purpose.

Tests described in the USP are typically considered sufficient standards for establishing specified properties and characteristics of specified materials of construction or packaging components.

For non-USP tests, an applicant should provide justification for the use of the test, a complete and detailed description of how the test was performed, and an explanation of what the test is intended to establish. If a related USP test is available, comparative data should be provided using both methods. Supporting data should include a demonstration of the suitability of the test for its intended use and its validation.

Testing on an assembled container closure system is usually

performed by the applicant (or a testing laboratory commissioned by the applicant) and the test results provided in the application. Such tests may include vacuum leak testing, moisture permeation, and weight loss or media fill.

Testing on an individual packaging component is typically performed by the manufacturer of the component and reported via a DMF (see section V).

3. Information About Quality Control

The fabricator/manufacturer of a packaging component and the drug product manufacturer who uses this firm share the responsibility for ensuring the quality of packaging components. These firms should have a quality control program in place so that consistent components are produced. The drug product manufacturer must have an inspection program for incoming packaging components and materials (21 CFR 211.22, 211.84 and 211.122). For most drug products, a drug product manufacturer may accept a packaging component lot based on receiving a Certificate of Analysis (COA) or Certificate of Certification (COC) from the component supplier and the performance of an appropriate identification test, provided the supplier's test data are periodically validated (21 CFR 211.84(d)(3)). Acceptance of a packaging component lot based on a supplier's COA or COC may not be appropriate in all cases (e.g., some packaging components for certain inhalation drug products).

a. Applicants

The tests and methods used by the applicant for acceptance of each batch of a packaging component that they receive should be described. If a batch is to be accepted based on a supplier's COA or COC, then the procedure for supplier validation should be described. The data from the supplier's COA or COC should clearly indicate that the lot meets the applicant's acceptance criteria. Acceptance criteria for extractables should also be included, if appropriate.

Dimensional and performance criteria should be provided. Dimensional information is frequently provided via a detailed schematic drawing complete with target dimensions and tolerances and may be provided via the packaging component manufacturer's DMF. A separate drawing may not be necessary if the packaging component is part of a larger unit for which a drawing is provided or if the component is uncomplicated in design (e.g., a cap liner).

b. Manufacturers of Packaging Components Sold to Drug Product

Manufacturers

Each manufacturer of a packaging component sold to a drug product manufacturer should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the component. These generally include release criteria (and test methods, if appropriate) and a description of the manufacturing procedure. If the release of the packaging component is based on statistical process control,[18] a complete description of the process (including control criteria) and its validation should be provided.

The description of the manufacturing process is generally brief and should include any operations performed on the packaging component after manufacture but prior to shipping (e.g., washing, coating, and/or sterilization). In some cases it may be desirable for the description to be more detailed and to include in-process controls.

This information may be provided via a DMF (see section V).

c. Manufacturers of Materials of Construction or of Packaging Components Used to Make Other Packaging Components

The quality control procedures of the manufacturer of a packaging component may sometimes rely in whole or in part on the quality control procedures of a manufacturer who makes an intermediate packaging component that is used to create the component. If so, each contributor to the final packaging system should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the separate components and of the assembled packaging system that they provide.

The manufacturer of each material of construction should be prepared to describe the quality control measures used to maintain consistency in the chemical characteristics of their product.

This information may be provided via a DMF (see section V).

4. Stability Data (Packaging Concerns)

Stability testing of the drug product should be conducted using the container

[18] Statistical process control is defined as "[t]he application of statistical techniques for measuring and analyzing the variation in processes." Juran, J.M., ed., 1988, *Quality Control Handbook*, 4th ed., McGraw-Hill, p. 24.2.

closure systems proposed in the application. The packaging system used in each stability study should be clearly identified.

The container closure system should be monitored for signs of instability. When appropriate, an evaluation of the packaging system should be included in the stability protocol. Even when a formal test for quality of the packaging system is not performed, the applicant should investigate any observed change in the packaging system used in the stability studies. The observations, results of the investigation, and corrective actions should be included in the stability report. If the corrective action requires a change in an approved container closure system, a supplemental application should be submitted.

For general guidance on conducting stability studies, refer to the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987). The stability guideline is undergoing revision and will be superseded by the FDA's draft guidance for industry *Stability Testing of Drug Substance and Drug Products* (June 1998), once it is issued in final form.

**Table 3**

**Information That Should Be Submitted in an Original Application for Any Drug Product**

| | |
|---|---|
| **Description** | Overall general description of the container closure system, plus:<br><br>For Each Packaging Component:<br>• Name, product code, manufacturer, physical description<br>• Materials of construction (for each: name, manufacturer, product code)<br>• Description of any additional treatments or preparations |
| **Suitability** | Protection: (By each component and/or the container closure system, as appropriate)<br>• Light exposure<br>• Reactive gases (e.g., oxygen)<br>• Moisture permeation<br>• Solvent loss or leakage<br>• Microbial contamination(sterility/container integrity, increased bioburden, microbial limits)<br>• Filth<br>• Other<br><br>Safety: (for each material of construction, as appropriate)<br>• Chemical composition of all plastics, elastomers, adhesives, etc.[a]<br>• Extractables, as appropriate for the material[b]<br>Extraction/toxicological evaluation studies, as appropriate<br>Appropriate USP testing<br>Appropriate reference to the indirect food additive regulations (21 CFR 174-186)<br>• Other studies as appropriate<br><br>Compatibility: (for each component and/or the packaging system, as appropriate)<br>• Component/dosage form interaction, USP methods are typically accepted<br>• May also be addressed in post-approval stability studies<br><br>Performance: (for the assembled packaging system)<br>• Functionality and/or drug delivery, as appropriate |
| **Quality Control** | For Each Packaging Component Received by the Applicant:<br>• Applicant's tests and acceptance criteria[c]<br>• Dimensional (drawing) and performance criteria<br>• Method to monitor consistency in composition, as appropriate<br><br>For Each Packaging Component Provided by the Supplier:<br>• Manufacturer's acceptance criteria for release, as appropriate<br>• Brief description of the manufacturing process |
| **Stability** | • See section III.C.4 |

[a] Including any additives used in the manufacture of a packaging component

[b] See Attachment C for further discussion of extraction studies. Testing of plastics should be performed on the packaging component, not on the unformed resin. For a blow/fill/seal product, extractables should be evaluated on the formed drug product container itself. This also applies to a container closure system which is manufactured as part of the drug product manufacturing process.

[c] Note that an applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

## D. Inhalation Drug Products

Inhalation drug products include inhalation aerosols (metered dose inhalers); inhalation solutions, suspensions, and sprays (administered via nebulizers); inhalation powders (dry powder inhalers); and nasal sprays. The CMC and preclinical considerations for inhalation drug products are unique in that these drug products are intended for respiratory-tract compromised patients. This is reflected in the level of concern given to the nature of the packaging components that may come in contact with the dosage form or the patient (see Table 1).

Guidance regarding the container closure system information to support the approval of applications for inhalation drug products will be provided in two guidance documents when finalized: the guidance for industry *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry, Manufacturing and Controls Documentation* (a draft was issued in October 1998) and the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing and Controls Documentation,* which is currently under development.

## E. Drug Products for Injection and Ophthalmic Drug Products

These dosage forms share the common attributes that they are generally solutions, emulsions, or suspensions, and are all required to be sterile. Injectable dosage forms represent one of the highest risk drug products (see Table 1). Any contaminants present (as a result of contact with a packaging component or due to the packaging system's failure to provide adequate protection) can be rapidly and completely introduced into the patient's general circulation. Although the risk factors associated with ophthalmics are generally considered to be lower than for injectables, any potential for causing harm to the eyes demands caution.

### 1. Injectable Drug Products

Injectable drug products may be liquids in the form of solutions, emulsions, suspensions, or dry solids that are to be combined with an appropriate vehicle to yield a solution or suspension. Injections are classified as small-volume parenterals (SVPs), if they have a solution volume of 100 mL or less, or as large-volume parenterals (LVPs), if the solution volume exceeds 100 mL.[19] For solids that must be dissolved or dispersed in an appropriate diluent before being injected, the diluent may be in the same container closure system (e.g., a two-part vial) or be part of the same market package (e.g., a kit containing a vial of diluent).

[19] The terms SVP and LVP as used in this guidance correspond to the definitions of small-volume injection and large-volume injection, respectively, in USP 23, page 1650.

An SVP may be packaged in a disposable cartridge, a disposable syringe, a vial, an ampule or a flexible bag. An LVP may be packaged in a vial, a flexible bag, a glass bottle or, in some cases, as a disposable syringe.

Cartridges, syringes, vials, and ampules are usually composed of Type I or II glass, or polypropylene. Flexible bags are typically constructed with multilayered plastic. Stoppers and septa in cartridges, syringes, and vials are typically composed of elastomeric materials. The input (medication) and output (administration) ports for flexible bags may be plastic and/or elastomeric materials. An overwrap may be used with flexible bags to retard solvent loss and to protect the flexible packaging system from rough handling.

The potential effects of packaging component/dosage form interactions are numerous. Hemolytic effects may result from a decrease in tonicity and pyrogenic effects may result from the presence of impurities. The potency of the drug product or concentration of the antimicrobial preservatives may decrease due to adsorption or absorption. A cosolvent system essential to the solubilization of a poorly soluble drug can also serve as a potent extractant of plastic additives. A disposable syringe may be made of plastic, glass, rubber, and metal components, and such multicomponent construction provides a potential for interaction that is greater than when a container consists of a single material.

Injectable drug products require protection from microbial contamination (loss of sterility or added bioburden) and may also need to be protected from light or exposure to gases (e.g., oxygen). Liquid-based injectables may need to be protected from solvent loss, while sterile powders or powders for injection may need to be protected from exposure to water vapor. For elastomeric components, data showing that a component meets the requirements of USP Elastomeric Closures for Injections will typically be considered sufficient evidence of safety. For plastic components, data from USP Biological Reactivity Tests will typically be considered sufficient evidence of safety. Whenever possible, the extraction studies should be performed using the drug product. If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing accipient), then drug product should be used as the extracting medium. If the drug substance significantly affects extraction characteristics, it may be necessary to perform the extractions using the drug product vehicle. If the total of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. It may be advisable to obtain a quantitative extraction profile of an elastomeric or plastic packaging component and to compare this periodically to the profile from a new batch of the packaging component. Extractables should be identified whenever possible. For a glass packaging component, data from USP Containers: Chemical Resistance — Glass Containers will typically be considered sufficient evidence of safety and compatibility. In some cases (e.g., for some chelating

agents), a glass packaging component may need to meet additional criteria to ensure the absence of significant interactions between the packaging component and the dosage form.

Performance of a syringe is usually addressed by establishing the force to initiate and maintain plunger movement down the barrel, and the capability of the syringe to deliver the labeled amount of the drug product.

2. Ophthalmic Drug Products

These drug products are usually solutions marketed in a LDPE bottle with a dropper built into the neck (sometimes referred to as *droptainer*), or ointments marketed in a metal tube with an ophthalmic tip (see section III.F.2 for a more detailed discussion of tubes). A few solution products use a glass container due to stability concerns regarding plastic packaging components. Ophthalmic ointments that are reactive toward metal may be packaged in a tube lined with an epoxy or vinyl plastic coating. A large volume intraocular solution (for irrigation) may be packaged in a glass or polyolefin (polyethylene and/or polypropylene) container.

The American Academy of Ophthalmology (AAO) recommended to the Agency that a uniform color coding system be established for the caps and labels of all topical ocular medications. An applicant should either follow this system or provide an adequate justification for any deviations from the system. The AAO color codes, as revised and approved by the AAO Board of Trustees in June 1996, are shown in Table 5.

Although ophthalmic drug products can be considered topical products (section III.F.2), they have been grouped here with injectables because they are required to be sterile (21 CFR 200.50(a)(2)) and the descriptive, suitability, and quality control information is typically the same as that for an injectable drug product. Since ophthalmic drug products are applied to the eye, compatibility and safety should also address the container closure system's potential to form substances which irritate the eye or introduce particulate matter into the product (see USP <771> Ophthalmic Ointments).

See Table 4 for additional information.

**Table 4**
**Information That Typically Should Be Submitted for Injectable or Ophthalmic Drug Products**

| | |
|---|---|
| **Description** | Overall general description of container closure system, plus:<br><br>For Each Packaging Component:<br>• Name, product code, manufacturer, physical description<br>• Materials of construction (for each: name, manufacturer and product code)<br>• Description of any additional treatments (e.g., procedures for sterilizing and depyrogenating packaging components) |
| **Suitability** | Protection: (By each component and/or the container closure system, as appropriate)<br>• Light exposure, when appropriate<br>• Reactive gases (e.g., oxygen)<br>• Moisture permeation (powders)<br>• Solvent loss (liquid-based dosage forms)<br>• Sterility (container integrity) or increased bioburden<br>• Seal integrity or leak testing of tubes (ophthalmics)<br><br>Safety: (for each material of construction, as appropriate)<br>• Chemical composition of all plastics, elastomers, adhesives, etc.[a]<br>• For elastomeric closures: USP Elastomeric Closures for Injections testing<br>• For glass components: USP Containers: Chemical Resistance — Glass Containers<br>• For plastic components and coatings for metal tubes: USP Biological Reactivity Tests<br>• If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium.<br>• If the total weight of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained.<br>• For plastic or elastomeric components undergoing heat sterilization, it is current practice to request that the extraction profile be obtained at 121°C/1 hour using an appropriate solvent.<br><br>Compatibility: (for each component and/or the packaging system, as appropriate)<br>• For coatings on metal tubes: Coating integrity testing<br>• For elastomeric components: Evaluation of swelling effects<br>• For plastic components (including tube coatings): USP Containers: Physicochemical Tests - Plastics testing<br>• For ophthalmics: Particulate matter and eye irritants<br>• Stability studies also support compatibility<br><br>Performance: (For the assembled packaging system)<br>• Functionality and/or drug delivery |

| | |
|---|---|
| **Quality Control** | <u>For Each Packaging System Received by the Applicant</u>:<br>• Applicant's tests and acceptance criteria[c]<br>• Dimensional (drawing) and performance criteria<br>• Method to monitor consistency in composition of most plastic and elastomeric components (e.g., periodic comparison to the original extraction profile is recommended)<br><br><u>For Each Packaging Component Provided by the Supplier</u>:<br>• Manufacturer's acceptance criteria for release, as appropriate<br>• Description of the manufacturing process, as appropriate (e.g., procedure/validation for sterilization and depyrogenation) |
| **Stability** | • See section III.C.4 |

a. Including any additives used in the manufacture of a packaging component

b. Testing for plastics should be performed on the packaging component, not on the unformed resin.

c. Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

d Refer to the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug* (November 1994).

**Table 5**
**AAO Recommended Color Coding of Caps and Labels for Topical Ophthalmic Medications**

| Class | Color | Pantone® Number |
|---|---|---|
| Anti-Infectives | Tan | 467 |
| Anti-Inflammatories/Steroids | Pink | 197, 212 |
| Mydriatics and Cycloplegics | Red | 485C |
| Nonsteroidal Anti-Inflammatories | Gray | 4C |
| Miotics | Green | 374, 362, 348 |
| Beta-Blockers | Yellow or Blue[a]<br>Yellow C | 290, 281 |
| Adrenergic Agonists (e.g., Propine) | Purple | 2583 |
| Carbonic Anhydrase Inhibitors | Orange | 1585 |
| Prostaglandin Analogues | Turquoise | 326C |

a The AAO notes that as new classes of drugs are developed this coding system may be modified in the future by reassigning the blue color to a new class of drugs while keeping yellow for beta-blockers.

## F. Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems

A wide variety of drug products fall into this category. The presence of a liquid phase implies a significant potential for the transfer of materials from a packaging component into the dosage form. The higher viscosity of semisolid dosage forms and transdermal systems may cause the rate of migration of leachable substances into these dosage forms

to be slower than for aqueous solutions. Due to extended contact, the amount of leachables in these drug products may depend more on a leachable material's affinity for the liquid/semisolid phase than on the rate of migration.

1. Liquid-Based Oral Drug Products

Typical liquid-based oral dosage forms are elixirs, emulsions, extracts, fluid extracts, solutions, gels, syrups, spirits, tinctures, aromatic waters, and suspensions. These products are usually nonsterile but may be monitored for changes in bioburden or for the presence of specific microbes.

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 overcap that is welded to the bottle. The same cap liners and inner seals are sometimes used with solid oral dosage forms. A pouch may be a single-layer plastic or a laminated material. Both bottles and pouches 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.

A liquid-based oral drug product typically needs to be protected from solvent loss, microbial contamination, and sometimes from exposure to light or reactive gases (e.g., oxygen).

For glass components, data showing that a component meets the requirements of USP Containers: Glass Containers are accepted as sufficient evidence of safety and compatibility. For LDPE components, data from USP Containers tests are typically considered sufficient evidence of compatibility. The USP General Chapters do not specifically address safety for polyethylene (HDPE or LDPE), polypropylene (PP), or laminate components. A patient's exposure to substances extracted from a plastic packaging component (e.g., HDPE, LDPE, PP, laminated components) into a liquid-based oral dosage form is expected to be comparable to a patient's exposure to the same substances through the use of the same material when used to package food. Based on this assumption, an appropriate reference to the indirect food additive regulations (21 CFR 174-186)[20] is typically considered sufficient to establish 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 which the patient will take only for a relatively short time (acute dosing regimen).

[20] See Attachment A for a listing of the FDA regulations for indirect food additives.

For liquid-based oral drug products which the patient will continue to take for an extended period (i.e., months or years (chronic drug regimen)), 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 can be expected to be no greater than the exposure through foods, or 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.

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), then additional extractable information[21] may be needed to address safety issues.

Performance is typically not a factor for liquid-based oral drug products.

See Table 6 for additional information.

2. Topical Drug Products

Topical dosage forms include aerosols, creams, emulsions, gels, lotions, ointments, pastes, powders, solutions, and suspensions. These dosage forms are generally intended for local (not systemic) effect and are generally applied to the skin or oral mucosal surfaces. Topical products also include some nasal and otic preparations as well as some ophthalmic drug products. Ophthalmic drug products are discussed in section III.E.2. Vaginal and rectal drug products may be considered to be topical if they are intended to have a local effect. Some topical drug products are sterile or may be subject to microbial limits. In these cases, additional evaluation may be necessary when determining the appropriate packaging.

A liquid-based topical product typically has a fluid or semi-solid consistency and is marketed in a single- or multiple-unit container (e.g., a rigid bottle or jar, a collapsible tube, or a flexible pouch). A powder product may be marketed in a sifter-top container. An antibacterial product may be marketed as part of a sterile dressing. There are also a number of products marketed as a pressurized aerosol or a hand-pumped spray.

A rigid bottle or jar is usually made of glass or polypropylene with a screw cap.

---

[21] See Attachment C for a discussion of extraction studies.

The same cap liners and inner seals are sometimes used as with solid oral dosage forms.

A collapsible tube is usually constructed from metal or is metal-lined, from LDPE or from a laminated material. Tubes are identified as either *blind-end* or *open-end.* In the former, there is no product contact with the cap on storage. Usually, the size of the tube is controlled by trimming it to an appropriate length for the target fill volume. Fill volume is commonly determined as an in-process measurement using bulk density. Usually there is no cap liner, although the tube may have a liner. Aluminum tubes usually include a liner. A tube liner is frequently a lacquer or shellac whose composition should be stated. A tube is closed by folding or crimping the open end. The type of fold (roll or saddle) should be described, as well as the type and composition of any sealant. If the tube material is self-sealing through the application of heat alone, this should be stated. If the market package includes a separate applicator device, this should be described. Product contact is possible if the applicator is part of the closure, and therefore an applicator's compatibility with the drug product should be established, as appropriate.

Dressings consist of dosage form on a bandage material (e.g., Absorbent Gauze USP or Gauze Bandage USP) within a flexible pouch. The pouch should maintain the sterility and physical stability of the dressing.

Unlike inhalation aerosols, topical aerosols are not intended to be inhaled. The droplet size of the spray does not need to be carefully controlled, nor is the dose usually metered. The spray may be used to apply dosage form to the skin (topical aerosol) or mouth (lingual aerosol) and functionality of the sprayer should be addressed. A topical aerosol may be sterile or may conform to acceptance criteria for microbial limits.

The packaging system for a liquid-based topical product should deter solvent loss and should provide protection from light when appropriate. Because these dosage forms may be placed in contact with mucosal membranes or with skin that has been broken or otherwise compromised, the safety of the materials of construction for the packaging components should be evaluated. For liquid and semisolid dosage forms, the same information as described in section III.F.1 is accepted for establishing safety and compatibility. For solid dosage forms, an appropriate reference to the indirect food additive regulations is typically considered sufficient to establish safety.

See Table 6 for additional information.

3. Topical Delivery Systems

Topical delivery systems are self-contained, discrete dosage forms that are

designed to deliver drug via intact skin or body surface. USP Pharmaceutical Dosage Forms defines three types of topical delivery systems: transdermal, ocular, and intrauterine.

Transdermal systems are usually applied to the skin with an adhesive and may be in place for an extended period. Ocular systems are inserted under the lower eyelid, typically for seven days. Intrauterine systems are held in place without adhesive and may stay in place for a year.

A transdermal system is usually comprised of an outer barrier, a drug reservoir (with or without a rate-controlling membrane), a contact adhesive, and a protective liner. An ocular system usually consists of the drug formulation contained in a rate-controlling membrane. An intrauterine system may be constructed of a plastic material impregnated with active ingredients or a coated metal. It is shaped to remain in place after being inserted in the uterus.

Each of these systems is generally marketed in a single-unit soft blister pack or a preformed tray with a preformed cover or overwrap.

Compatibility and safety for topical delivery systems are addressed in the same manner as for topical drug products. Performance and quality control should be addressed for the rate-controlling membrane. Appropriate microbial limits should be established and justified for each delivery system. Microbiological standards are under development; therefore the review division for a specific application should be consulted.

See Table 6 for additional information.

**Table 6**
**Information That Typically Should Be Submitted for Liquid-Based Oral and Topical Drug Products and for Topical Drug Delivery Systems**

| | |
|---|---|
| **Description** | Overall general description of container closure system, plus:<br><br>For Each Packaging Component:<br>• Name, product code, manufacturer, physical description<br>• Materials of construction (for each: name, manufacturer and product code)<br>• Description of any additional treatments (e.g., procedure for washing components) |
| **Suitability** | Protection: (by each component and/or the container closure system, as appropriate)<br>• Light exposure<br>• Reactive gases (e.g., oxygen)<br>• Solvent loss<br>• Moisture permeation (liquid-based oral products would typically meet USP requirements for a tight or class A container)<br>• Microbial contamination (container integrity, increased bioburden, microbial limits, as appropriate)<br>• Seal integrity or leak testing of tubes (topical drug products) and unit dose containers (liquid-based oral drug products)<br><br>Safety: (for each material of composition, as appropriate)<br>• Chemical composition of all plastics, elastomers, adhesives, etc.[a]<br>• For most liquid-based oral drug products: appropriate reference to the indirect food additive regulations<br>• For liquid-based oral drug products with chronic dosing regimens that contain alcohol or a cosolvent: information to establish that exposure to extractables will be no greater than that expected to result from the use of similar packaging components when used with foods,[b] or that the exposure is acceptable based on toxicological data.<br>• For topical drug products (plastic coatings for metal tubes), and plastic drug delivery system components: USP Containers testing<br>• For topical delivery systems: appropriate reference to indirect food additive regulations<br><br>Compatibility: (for each component of the packaging system, as appropriate)<br>• For LDPE and glass components, USP Containers testing[c]<br>• For coatings for metal tubes: coating integrity testing<br><br>Performance: (for the assembled packaging system)<br>• Functionality and/or drug delivery should be addressed, as appropriate. |
| **Quality Control** | For Each Packaging Component Received by the Applicant:<br>• Applicant's tests and acceptance criteria[d]<br>• Dimensional (drawing) and performance criteria<br>• Method to monitor consistency in composition, as appropriate<br><br>For Each Packaging Component Provided by the Supplier:<br>• Manufacturer's acceptance criteria for release, as appropriate<br>• Description of the manufacturing process, as appropriate |

| | |
|---|---|
| **Stability** | • See section III.C.4 |

[a] Including any additives used in the manufacture of a packaging component

[b] The materials of construction should be acceptable for contact with foods that have extraction characteristics similar to those of the drug product (e.g., aqueous, acidic, alcoholic, or fatty).

[c] Plastics testing should be performed on the packaging component, not on the unformed resin.

[d] Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

## G. Solid Oral Dosage Forms and Powders for Reconstitution

The most common solid oral dosage forms are capsules and tablets. For the purpose of this guidance, oral powders and granules for reconstitution are also included in this group.

The risk of interaction between packaging components and a solid oral dosage form is generally recognized to be small. Powders that are reconstituted in their market container, however, have an additional possibility of an interaction between the packaging components and the reconstituting fluid. Although the contact time will be relatively short when compared to the component/dosage form contact time for liquid-based oral dosage forms, it should still be taken into consideration when the compatibility and safety of the container closure system is being evaluated.

A typical container closure system is a plastic (usually HDPE) bottle with a screw-on or snap-off closure and a flexible packaging system, such as a pouch or a blister package. A typical closure consists of a cap, often with a liner, and frequently with an inner seal. If used, fillers, desiccants, and other absorbent materials are considered primary packaging components.

The most common forms of flexible packaging are the blister package and the pouch. A blister package usually consists of a lidding material and a forming film. The lidding material is usually a laminate 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 agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. A pouch typically consists of film or laminate which is sealed at the edges by heat or adhesive. Leak testing is usually performed on flexible packages as part of the in-process controls.

Solid oral dosage forms generally need to be protected from the potential adverse affects of water vapor. Protection from light and reactive gases may also be needed. For example the presence of moisture may affect the decomposition rate of the active drug substance or the dissolution rate of the dosage form. The container should have an intrinsically low rate of water vapor permeation, and the container closure system should establish a seal to protect the drug product. Three standard tests for water vapor permeation have been established by the USP for use with solid oral dosage forms.

1. Polyethylene Containers (USP <661>): This test is conducted on containers heat-sealed with foil laminate; therefore only the properties of the container are evaluated. The level of protection from water vapor permeation provided by a packaging system marketed with a heat-sealed foil laminate inner seal (up to the time the inner seal is removed) is expected to be approximately the same as that determined by this test. The acceptance criteria are those established in USP <671>.

2. Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (USP <671>): This test measures the water vapor permeation of a single-unit or unit-dose container closure system and establishes acceptance criteria for five standards (*Class A-E* containers).

3. Multiple-Unit Containers for Capsules and Tablets (USP <671>): This test is intended for drugs being dispensed on prescription, but has also been applied to the drug product manufacturer's container closure system. If the container closure system has an inner seal, it should be removed prior to testing. The results from this study reflect the contributions to water vapor permeation through the container, and through the seal between the container and the closure. Acceptance criteria have been established for two standards (*tight* and *well-closed* containers).

For solid oral dosage forms, a reference to the appropriate indirect food additive regulation for each material of construction is typically considered sufficient evidence of safety. However, for a powder for reconstitution dosage form, reference only to the indirect food additive regulations as evidence of safety for the materials of construction is not recommended. Compatibility for solid oral dosage forms and for powders for reconstitution is typically addressed for plastics and glass by meeting the requirements of the USP Containers test.

The USP monographs for Purified Cotton and Purified Rayon will typically be considered sufficient standards to establish the safety of these materials as fillers in the packaging of tablets or capsules, with the following caveats: cotton need not meet the monograph requirements for sterility, fiber length, or absorbency; and rayon need not meet the monograph requirements for fiber length or absorbency. Appropriate tests and acceptance criteria for identification and for moisture content should be provided for both cotton and rayon filler. Rayon has been found to be a potential source of dissolution problems for gelatin capsules and gelatin-coated tablets and this characteristic should be considered when choosing a filler.[22] The use of other fillers may be considered with appropriate tests and acceptance criteria.

---

[22] Hartauer, K.J. et al., "The Effects of Rayon Coiler on the Dissolution Stability of Hard Shelled Gelatin Capsules," *Pharmaceutical Technology*, 17:76-83 (1993).