はゴム栓の持つ水分特性を十分な評価が必要であるとの認識から、空バイアル内にシリカゲルを充填して、各ゴム栓でシールしたものを検体として40℃90%RH環境下に保存し、検体全体、シリカゲル、ゴム栓の経時的な各重量変化から、ゴム栓の水分特性を評価した(図1)。

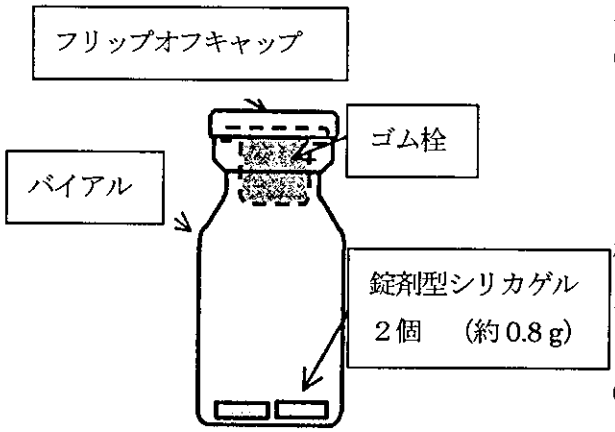

図　1　ゴム栓バイアル水分特性試験。参考文献（2）より引用。

水分特性評価では、水分透過性、水分含有量、水分含有能がそれぞれのゴム栓で大きく異なることが明らかとなった。　さらに水分含量が品質劣化となる薬剤を用いて評価したところ、水分透過が特に大きかったゴム栓との組み合わせでは、40℃75RH・3ヶ月保存後の含量が92.7%となった。品質劣化につながる凍結乾燥製剤は経時変化を含めた注意深い評価の必要性を喚起するとともに、上記の水分特性評価試験が有用であることを示した。

C2B ガラスバイアルと薬液との相互作用の研究（参考文献3）では“現在の日本薬局方の注射剤ガラス容器の規定では、あらゆる処方または製造工程に適するとは言えず、薬液とガラス容器との相互作用については十分な検討が必要”との認識から“製剤設計におけるガラスバイアルの選定方法の確立を目指し、材質、内面処理及び加工法の異なるバイアルについて、薬液並びに製造工程で暴露される熱負荷の違いによって生じる相互作用、特にフレークス発生の比較を”行ない“①ソーダライムガラスとホウケイ酸ガラスなどの材質、鋳型加工あるいは管加工といった加工法、並びにサルファー処理の違い②　注射用水、生理食塩水、実薬液など薬液の違い③感熱滅菌工程、高圧蒸気滅菌工程など製造工程が注射剤の品質に影響すること”を明らかにした。

ガラスバイアルの選定は加工法を含めた原材料の品質、製造工程、薬液を考慮した評価が必要と結論している。

C3　FDA 容器施栓系のガイダンス(添付資料イ)

申請資料のガイドラインであり、品質管理(GMP)手法を述べたものではないとしている。ガイドラインと異なることを行う場合は容器施栓系の評価は時間がかかるため、審査当局への事前相談を強く推奨している。（1ページ）

ガイドでは以下の定義している。（2ページ）

包装材料種(materials of construction)はガラス、高密度ポリエチレン樹脂、金属などである。

包装容器成分(packaging component)は容器施栓系の成分で、容器、シール、蓋・栓などである。

一次包装容器成分(primary packaging component)とは製剤形と直接接触するもの、あるいは接触する可能性のあるものである。二次包装容器成分(secondary packaging component)は製剤形と直接触れない、あるいは触れる可能性が決して無い容器成分である。

容器・施栓系(container closure system)とは製剤形を包含して、保護するすべての包装容器成分の総和であると規定している。

その上で容器・施栓は医薬品の製剤と組み合わせで考えるべきものであって、容器・施栓及び製

剤そのものを独立して考えるべきでないことを強調している。

容器は医薬品の有効期間を通し、医薬品の保護機能、製剤との適合性(compatibility)、安全性(safety)が適格性(suitability)評価の中心になるべきとしている。容器の適格性は投与ルートからのリスク・懸念（concern）の程度および剤型と一次包装との相互作用からくるリスクの大きさにより適格性評価の厳格性をもとめるべきとしている。（同　5ページ）

注射剤の容器・施栓系からの潜在的悪影響は、溶血、発熱、容器への吸着による薬剤・保存剤の低下、複合容器からの有害化学物質の溶出などがあることの注意を喚起している。　その上で、申請資料として、①すべての包装容器成分について製造元、製品番号など、②保護機能については、反応性ガス、水分透過性、無菌の完全性などを、③安全性については、包装容器成分の製造元で用いられるものを含むすべての化学組成情報、USP 要件、薬液への添加物の溶出などを、④適合性については、安定性試験などを、⑤品質管理については、受け入れ試験、ほとんどの包装容器成分の化学組成試験法などを、⑥安定試験には容器・施栓系を明らかにし実行することを、それぞれ提出を要求している。（同、２６ページ　Table 4）

一方で標準的な適格性プロトコールを決めることは簡単ではないとしている。その上で、安定性評価は全有効期間の事前申請データを要求せず、モニター手法を許容する立場をとっている。

C4 米国における変更申請手続き

Code of Federal Regulation 314.70 では容器・施栓系を支配する包装材のタイプ(例えば、ガラスから高密度ポリエチレンへ、高密度ポリエチレンからポリ塩化ビニルへ）の変更、又は製品の不純物プロファイルに影響を与える可能性のある包装成分（例えば、ある高密度ポリエチレンから高密度ポリエチレンへ）の変更は事前承認項目としている。

C5 医薬品品質フォーラムにおける議論

第二回医薬品品質フォーラムシンポジウムにおいて容器・施栓系の適格性評価の海外における手法、規制を紹介した。（添付資料　ロ）この中の議論において、①容器は製薬企業が設計・生産しているものでないこと②容器は製剤との組み合わせにおいて評価すべきであることから、①容器供給メーカーへ製薬企業からの要求事項の明確化②Vendor audit の重要性③マスターファイル制度の整備が課題として挙げられた。（添付資料　ハ、ニ）

C6 申請添付資料及び承認書記載

以上の調査結果からの論点をまとめると

①容器・施栓は製剤との組み合わせ（容器・施栓系）として評価するべきものである。したがって、ゴム栓、ガラスを一般評価すること、例えば薬局方の試験とすることだけでは不十分である。②容器・施栓系の評価は、製剤設計、製造法開発と並び医薬品の品質に重要な要素であるため、研究開発段階で想定されるリスクに応じて行われるべきものである。③容器・施栓系の評価情報、管理情報は恒常生産の要点であるので技術移転情報として必須である。①から③の論点は技術移転ガイドラインと研究事例から導くことができるが、これらの論点を FDA は認識した上でガイダンスを発行し、行政の変更手続きへ組み入れているものと思われる。

評価の厳密性は薬物固有特性にもよるが、容器・施栓系としてのリスクの程度に応じ行われるべきである。特に注射用の直接容器の評価は研究事例のような系統的な評価を製剤・製造工程開発段階、変更段階で行うべきである。申請添付資料の容器・施栓系の項には最終製品の安定性を含めた品質への評価を示し、製造・品質管理でどのような具体的は方策をとったのかを記述すべきである。

上記の調査・評価に基づき、容器・施栓系を

一般に承認書記載とし、一次容器の材料種を事前承認事項とすることを提案する。一方、剤型と相互作用を起こすリスクの小さい内服固形製剤の 1 次包装材に関しては届け出で変更可能とすることを提案する。

D 考察

わが国では容器・施栓系に関する評価資料の提出は従来あまり要求されておらず、又承認書レベルではゼロに近いコミットメントであった。このため、研究開発の専門家には容器・施栓系の重要性は認識されていたが、工場生産及び薬事法申請関係者にはあまり認識はされていなかったように思われる。

今後は評価方法の事例研究の共有などを通じ重要性の認識を広めることが必要であり、ICH Q8（参考文献4）のもとでの評価ガイドラインの制定も考慮に値すると思われる。

容器・施栓系の評価は Vendor と製薬企業の共同作業が必要とされること及び開発段階ですべてを網羅し実行することが困難であるため、リスクベース（参考文献5）の戦略を立て、効率的に適格性評価を行うことが品質保証の観点から重要である。これらを認識した上で、ある程度はリスクを受け入れる柔軟な行政運営が必要とも考えられる。

F．健康被害情報

なし。

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ニ 西畑利明、清原孝雄 "出発原料、原材料、容器・施栓系記載の品質保証への役割" 第二回医薬品質フォーラムシンポジウム 分科会問題点まとめ

添付資料

Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 1999

Guidance for Industry

Container Closure Systems for Packaging Human Drugs and Biologics

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1999

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GUIDANCE FOR INDUSTRY[1]

CONTAINER CLOSURE SYSTEMS FOR PACKAGING HUMAN DRUGS AND BIOLOGICS

CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION

I. INTRODUCTION

This document is intended to provide guidance on general principles[2] for submitting information on packaging materials used for human drugs and biologics.[3] This guidance supersedes the FDA *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics*, issued in February 1987 and the packaging policy statement issued in a letter to industry dated June 30, 1995 from the Office of Generic Drugs.[4] This guidance is not intended to describe the information that should be provided about packaging operations associated with drug product manufacture.

Approaches which differ from those described in this guidance may be followed, but the applicant is encouraged to discuss significant variations in advance with the appropriate CDER chemistry review staff or CBER review staff. This is to prevent applicants or sponsors from spending unnecessary time and effort in preparing a submission that the FDA may later determine to be unacceptable.

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[1] This guidance has been prepared by the Packaging Technical Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) and in conjunction with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on container closure systems for the packaging of human drugs and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] In general, this guidance does not suggest specific test methods and acceptance criteria (except for references to *The United States Pharmacopia* methods), nor does it suggest comprehensive lists of tests. These details should be determined based on good scientific principles for each specific container closure system for particular drug product formulations, dosage forms, and routes of administration. Acceptance criteria should be based on actual data for particular packaging components and container closure systems, and they should be set to ensure batch-to-batch uniformity of packaging components.

[3] As used in this guidance, the terms *drug* and *drug product* include biologics unless otherwise noted.

[4] The policy statement is a document titled *Container/Closure Information Which Should Be Provided In An ANDA/AADA* which was written by the Office of Generic Drugs/Packaging Advisory Group.

II. BACKGROUND

The Federal Food, Drug, and Cosmetic Act (the Act) mandates the need for adequate information related to packaging materials. Section 501(a)(3) of the Act states that a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health...." In addition, section 502 of the Act states that a drug is considered misbranded if there are packaging omissions. Also, section 505 of the Act requires a full description of the methods used in, and the facilities and controls used for, the packaging of drugs (see Attachment A).

Section 505(b)(1)(D) of the Act states that an application shall include a full description of the methods used in, the manufacturing, processing and packing of such drug. This includes facilities and controls used in the packaging a drug product.

A. Definitions[5]

Materials of construction[6] refer to the substances (e.g., glass, high density polyethylene (HDPE) resin, metal) used to manufacture a packaging component.

A *packaging component* means any single part of a container closure system. Typical components are containers (e.g., ampules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals (LVPs)), overwraps, administration accessories, and container labels. A *primary packaging component* means a packaging component that is or may be in direct contact with the dosage form. A *secondary packaging component* means a packaging component that is not and will not be in direct contact with the dosage form.

A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A *packaging system* is equivalent to a container closure system.

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[5] These definitions are intended to clarify the use of certain terms in this guidance only and are not intended to supersede the definitions of *container* and *package* as provided for in 21 CFR 600.3.

[6] This term is used in a general sense for the basic material, which should be defined in the application in terms of its specific chemical composition for a given drug application (e.g., the specific polymer and any additives used to make the material).

A *package* or *market package*[7] refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap). A market package is the article provided to a pharmacist or retail customer upon purchase and does not include packaging used solely for the purpose of shipping such articles.

Quality refers to the physical, chemical, microbiological, biological, bioavailability, and stability attributes that a drug product should maintain if it is to be deemed suitable for therapeutic or diagnostic use. In this guidance, the term is also understood to convey the properties of safety, identity, strength, quality, and purity (see 21 CFR 211.94(a)).

An *extraction profile* refers to the analysis (usually by chromatographic means) of extracts obtained from a packaging component. A *quantitative extraction profile* is one in which the amount of each detected substance is determined.

B. CGMP, CPSC and USP Requirements on Containers and Closures

Current good manufacturing practice (CGMP) requirements for the control of drug product containers and closures are included in 21 CFR Parts 210 and 211. A listing of the relevant sections is provided in Attachment A. In addition, a listing of Compliance Policy Guides that deal with packaging issues is provided in Attachment B. References in this guidance to CGMP regulations are provided for completeness. For additional information, refer to the *FDA Compliance Program Guidance Manual* for Pre-Approval Inspections/Investigations (7346.832) which describes specific responsibilities for CDER scientists and for field investigators.

The FDA requirement for tamper-resistant closures is included in 21 CFR 211.132 and the Consumer Product Safety Commission (CPSC) requirements for child-resistant closures are included in 16 CFR 1700. An outline of these and other applicable regulatory requirements is provided in Attachment A.

The United States Pharmacopeial Convention has established requirements for containers which are described in many of the drug product monographs in *The United States Pharmacopeia/National Formulary* (USP/NF). For capsules and tablets, these requirements generally relate to the design characteristics of the container (e.g., tight, well-closed or light-resistant). For injectable products, materials of construction are also addressed (e.g., "Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light"). These requirements are defined in the "General Notices and Requirements" (Preservation, Packaging, Storage, and Labeling) section of the *USP*. The requirements for materials of construction are defined in the "General Chapters" of

[7] The materials of construction used in the labeling are a concern from a packaging perspective if they affect the protection and/or safety of the drug product.

the USP (see Attachment A).

C. Additional Considerations

1. Submissions of INDs

The packaging information in the chemistry, manufacturing, and controls section of an IND usually includes a brief description of the components, the assembled packaging system and any precautions needed to ensure the protection and preservation of the drug substance and drug product during their use in the clinical trials.

For general guidance regarding the container closure system information to be submitted for phase 1 studies, refer to the FDA guidance for industry *Content and Format of investigational New Drug Applications(INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995).

General guidance regarding the container closure system information to be submitted for phase 2 or phase 3 studies will be provided in the FDA guidance for industry *INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry, Manufacturing, and Controls Content and Format,* when finalized (draft guidance published April 21, 1999).

2. Submissions on Packaging of a Drug Product by Another Firm

a. Contract Packager

A contract packager is a firm retained by the applicant to package a drug product. The applicant remains responsible for the quality of the drug product during shipping, storage, and packaging.

The information regarding the container closure system used by a contract packager that should be submitted in the CMC section of an application (NDA, ANDA, or BLA), or in a DMF which is referenced in the application, is no different from that which would be submitted if the applicant performed its own packaging operations. If the information is provided in a DMF, then a copy of the letter of authorization (LOA) for the DMF should be provided in the application (see section V.A).

b. Repackager[8]

A repackager is a firm that buys drug product from the drug product manufacturer or distributor and repackages it for sale under a label different from that of the manufacturer. The repackager is responsible for ensuring the quality and stability of the repackaged drug prpoduct. The repackaging operation is required to e in compliance with CGMPs (21 CFR Part 211), and there are limits to the expiration period that may be used with the repackaged product unless the repackager conducts stability studies.[9] Packaging qualification information is not required if the repackager uses the same container closure system approved in the original application.

All significant phases of the manufacturing and processing of a drug product (including packaging) should be described as part of the CMC section of an application (NDA, ANDA or BLA), or in a DMF referenced in the application. The only exception is the repackaging of solid oral drug products for which an approved application already exists.[10] For biologics, repackaging is considered a step in the manufacturing process for which licensing is required (21 CFR 600.3(u) and 601).

III. QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS

A. Introduction

CDER and CBER approve a container closure system to be used in the packaging of a human drug or biologic as part of the application (NDA, ANDA or BLA) for the drug or biologic. A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application should contain enough information to show that each proposed container closure system and its components are suitable for its intended use.

The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug

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[8] This discussion does not apply to the repackaging of drug products for dispensing under the practice of pharmacy.

[9] FDA *Compliance Policy Guides*, "Expiration Dating of Unit Repackaged Drugs," 480.200, February 1, 1984, rev. March 1995 (CPG 7132b.11).

[10] FDA *Compliance Policy Guides*, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulation," 446.100, January 18, 1991 (CPG 7132c.06).

product for inhalation is often more detailed than that which should be provided about a packaging system for a solid oral dosage form. More detailed information usually should be provided for a liquid-based dosage form than for a powder or a solid, since a liquid-based dosage form is more likely to interact with the packaging components.

Table 1 illustrates the correlation between the degree of concern regarding the route of administration with the likelihood of packaging component-dosage form interactions for different classes of drug products.

Table 1
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	**Likelihood of Packaging Component-Dosage Form Interaction**		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

[a] For the purposes of this table, the term *suspension* is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.

For the purpose of this guidance, container closure systems for the most common types of dosage forms will be discussed in terms of five general categories: Inhalation Drug Products (section III.D); Drug Products for Injection and Ophthalmic Drug Products (Section III.E); Liquid-based Oral and Topical Drug Products and Topical Delivery Systems (section III.F); Solid Oral Dosage Forms and Powders for Reconstitution (section

III.G); and Other Dosage Forms (section III.H).

B. General Considerations

Suitability refers to the tests and studies used and accepted for the initial qualification of a component or a container closure system for its intended use. *Quality control* (QC) refers to the tests typically used and accepted to establish that, after the application is approved, the components and the container closure system continue to possess the characteristics established in the suitability studies. The subsections on *associated components* and *secondary components* describe the tests and studies for establishing suitability and quality control for these types of components. However, the ultimate proof of the suitability of the container closure system and the packaging process is established by full shelf life stability studies.

1. Suitability for the Intended Use

Every proposed packaging system should be shown to be *suitable* for its intended use: it should adequately *protect* the dosage form; it should be *compatible* with the dosage form; and it should be composed of materials that are considered *safe* for use with the dosage form and the route of administration. If the packaging system has a *performance* feature in addition to containing the product, the assembled container closure system should be shown to function properly.

Information intended to establish suitability may be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the firm. An adequately detailed description of the tests, methods, acceptance criteria, reference standards, and validation information for the studies should be provided. The information may be submitted directly in the application or indirectly by reference to a DMF. If a DMF is used, a letter authorizing reference (i.e., letter of authorization (LOA)) to the DMF must be included in the application (see section V.A).

General issues concerning protection, compatibility, safety and performance of packaging components and/or systems are discussed below. In this guidance, component functionality and drug delivery will also be addressed in connection with specific dosage forms and routes of administration (see sections III.D, III.E, III.F, III.G, and III.H).

a. Protection

A container closure system should provide the dosage form with adequate protection from factors (e.g., temperature, light) that can cause a degradation in the quality of that dosage form over its shelf life. Common causes of such degradation are: exposure to light, loss of solvent, exposure

to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination. A drug product can also suffer an unacceptable loss in quality if it is contaminated by filth.

Not every drug product is susceptible to degradation by all of these factors. Not all drug products are light sensitive. Not all tablets are subject to loss of quality due to absorption of moisture. Sensitivity to oxygen is most commonly found with liquid-based dosage forms. Laboratory studies can be used to determine which of these factors actually have an influence on a particular drug product.

Light protection[11] is typically provided by an opaque or amber-colored container or by an opaque secondary packaging component (e.g., cartons or overwrap). The USP test for light transmission (USP <661>) is an accepted standard for evaluating the light transmission properties of a container. Situations exist in which solid and liquid-based oral drug products have been exposed to light during storage because the opaque secondary packaging component was removed, contrary to the approved labeling and the USP monograph recommendation. A firm, therefore, may want to consider using additional or alternate measures to provide light protection to these drug products when necessary.

Loss of solvent can occur through a permeable barrier (e.g., a polyethylene container wall), through an inadequate seal, or through leakage. Leaks can develop through rough handling or from inadequate contact between the container and the closure (e.g., due to the buildup of pressure during storage). Leaks can also occur in tubes due to a failure of the crimp seal.

Water vapor or reactive gases (e.g., oxygen) may penetrate a container closure system either by passing through a permeable container surface (e.g., the wall of a low density polyethylene (LDPE) bottle) or by diffusing past a seal. Plastic containers are susceptible to both routes. Although glass containers would seem to offer better protection, because glass is relatively impermeable, glass containers are more effective only if there is a good seal between the container and the closure.

Protection from microbial contamination is provided by maintaining adequate container integrity after the packaging system has been sealed. An adequate and validated procedure should be used for drug product manufacture and packaging.

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[11] For further information regarding photostability studies, see the FDA *Guideline for the Photostability Testing of New Drug Substances and Products* (May 1997).

b. Compatibility

Packaging components that are compatible with a dosage form will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component.

Examples of interactions include loss of potency due to absorption or adsorption of the active drug substance, or degradation of the active drug substance induced by a chemical entity leached from a packaging component; reduction in the concentration of an excipient due to absorption, adsorption or leachable-induced degradation; precipitation; changes in drug product pH; discoloration of either the dosage form or the packaging component; or increase in brittleness of the packaging component.

Some interactions between a packaging component and dosage form will be detected during qualification studies on the container closure system and its components. Others may not show up except in the stability studies. Therefore, any change noted during a stability study that may be attributable to interaction between the dosage form and a packaging component should be investigated and appropriate action taken, regardless of whether the stability study is being conducted for an original application, a supplemental application, or as fulfillment of a commitment to conduct postapproval stability studies.

c. Safety

Packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product. This consideration is especially important for those packaging components which may be in direct contact with the dosage form, but it is also applicable to any component from which substances may migrate into the dosage form (e.g., an ink or adhesive).

Making the determination that a material of construction used in the manufacture of a packaging component is safe for its intended use is not a simple process, and a standardized approach has not been established. There is, however, a body of experience which supports the use of certain approaches that depend on the route of administration and the likelihood of interactions between the component and the dosage form (see Table 1).

For a drug product such as an injection, inhalation, ophthalmic, or transdermal, a comprehensive study is appropriate. This involves two

parts: first, an extraction study[12] on the packaging component to determine which chemical species may migrate into the dosage form (and at what concentration); and, second, a toxicological evaluation of those substances which are extracted to determine the safe level of exposure via the label specified route of administration. This technique is used by the Center for Food Safety and Applied Nutrition (CFSAN) to evaluate the safety of substances that are proposed as indirect food additives (e.g., polymers or additives that may be used in for packaging foods).[13]

The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).

For many injectable and ophthalmic drug products (see sections III.E and III.F), data from the USP Biological Reactivity Tests and USP Elastomeric Closures for Injections tests will typically be considered sufficient evidence of material safety.

For many solid and liquid oral drug products, an appropriate reference to the indirect food additive regulations (21 CFR 174-186) promulgated by CFSAN for the materials of construction used in the packaging component will typically be considered sufficient. Although these regulations do not specifically apply to materials for packaging drug products, they include purity criteria and limitations pertaining to the use of specific materials for packaging foods that may be acceptable for the evaluation of drug product packaging components. Applicants are cautioned that this approach may not be acceptable for liquid oral dosage forms intended for chronic use (see section III.F.1).

For drug products that undergo clinical trials, the absence of adverse reactions traceable to the packaging components is considered supporting evidence of material safety.

Safety assessments for specific dosage forms are discussed further in section III of this guidance.

d. Performance

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[12] See Attachment C for discussion of extraction studies.

[13] FDA/CFSAN, *Recommendations for Chemistry Data for Indirect Food Additive Petitions*, Version 1.2, Chemistry Review Branch, Office of Pre-Market Approval, June 1995.

Performance of the container closure system refers to its ability to function in the manner for which it was designed. A container closure system is often called upon to do more than simply contain the dosage form. When evaluating performance, two major considerations are container closure system functionality and drug delivery.

i. Container Closure System Functionality

The container closure system may be designed to improve patient compliance (e.g., a cap that contains a counter), minimize waste (e.g., a two-chamber vial or IV bag), improve ease of use (e.g., a prefilled syringe), or have other functions.

ii. Drug Delivery

Drug delivery refers to the ability of the packaging system to deliver the dosage form in the amount or at the rate described in the package insert. Some examples of a packaging system for which drug delivery aspects are relevant are a prefilled syringe, a transdermal patch, a metered tube, a dropper or spray bottle, a dry powder inhaler, and a metered dose inhaler.

Container closure system functionality and/or drug delivery are compromised when the packaging system fails to operate as designed. Failure can result from misuse, faulty design, manufacturing defect, improper assembly, or wear and tear during use. Tests and acceptance criteria regarding dosage form delivery and container closure system functionality should be appropriate to the particular dosage form, route of administration, and design features.

e. Summary

Table 2 summarizes typical packaging suitability considerations for common classes of drug products.

Table 2
Typical Suitability Considerations for Common Classes of Drug Products
(This table is a general guide, and is not comprehensive. See sections III.C through III.H for a more detailed discussion.)

Route of Administration/ Dosage Form	SUITABILITY[a]			
	Protection	**Compatibility**	**Safety**	**Performance/ Drug Delivery**
Inhalation Aerosols and Solutions, Nasal Sprays	L, S, M, W, G	Case 1c	Case 1s	Case 1d
Inhalation Powders	L, W, M	Case 3c	Case 5s	Case 1d
Injections, Injectable Suspensions[b]	L, S, M, G	Case 1c	Case 2s	Case 2d
Sterile Powders and Powders for Injection	L, M, W	Case 2c	Case 2s	Case 2d
Ophthalmic Solutions and Suspensions	L, S, M, G	Case 1c	Case 2s	Case 2d
Topical Delivery Systems	L, S	Case 1c	Case 3s	Case 1d
Topical Solutions and Suspensions, and Topical and Lingual Aerosols	L, S, M	Case 1c	Case 3s	Case 2d
Topical Powders	L, M, W	Case 3c	Case 4s	Case 3d
Oral Solutions and Suspensions	L, S, M	Case 1c	Case 3s	Case 2d
Oral Powders	L, W	Case 2c	Case 3s	Case 3d
Oral Tablets and Oral (Hard and Soft Gelatin) Capsules	L, W	Case 3c	Case 4s	Case 3d

[a] If there is a special performance *function* built into the drug product (e.g., counter cap), it is of importance for any dosage form/route of administration to show that the container closure system performs that function properly.

[b] For definition of the term *suspension*, see footnote a to Table 1.

Explanation of Codes in Table 2:

Protection:

L (protects from light, if appropriate)
S (protects from solvent loss/leakage)
M (protects sterile products or those with microbial limits from microbial contamination)
W (protects from water vapor, if appropriate)
G (protects from reactive gases, if appropriate)

Compatibility:

Case 1c: Liquid-based dosage form that conceivably could interact with its container closure system components (see examples described in section III.B.1).

Case 2c: Solid dosage form until reconstituted; greatest chance for interacting with its container closure system components occurs after it is reconstituted.

Case 3c: Solid dosage form with low likelihood of interacting with its container closure system components.

Safety:

Case 1s: Typically provided are USP Biological Reactivity Test data, extraction/toxicological evaluation, limits on extractables, and batch-to-batch monitoring of extractables.

Case 2s: Typically provided are USP Biological Reactivity Test data and possibly extraction/toxicological evaluation.

Case 3s: Typically, an appropriate reference to the indirect food additive regulations is sufficient for drug products with aqueous-based solvents. Drug products with non-aqueous based solvent systems or aqueous based systems containing co-solvents generally require additional suitability information (see section III.F).

Case 4s: Typically, an appropriate reference to the indirect food additive regulations is sufficient.

Case 5s: Typically, an appropriate reference to the indirect food additive regulations for all components except the mouthpiece for which USP Biological Reactivity Test data is provided.

Performance:

Case 1d: Frequently a consideration.
Case 2d: May be a consideration.
Case 3d: Rarely a consideration.

2. Quality Control of Packaging Components

In addition to providing data to show that a proposed container closure system is suitable for its intended use, an application should also describe the quality control measures that will be used to ensure consistency in the packaging components (see section III.C.3). These controls are intended to limit unintended postapproval

variations in the manufacturing procedures or materials of construction for a packaging component and to prevent adverse affects on the quality of a dosage form.

Principal consideration is usually given to consistency in physical characteristics and chemical composition.

a. Physical Characteristics

The physical characteristics of interest include dimensional criteria (e.g., shape, neck finish, wall thickness, design tolerances), physical parameters critical to the consistent manufacture of a packaging component (e.g., unit weight), and performance characteristics (e.g., metering valve delivery volume, or the ease of movement of syringe plungers). Unintended variations in dimensional parameters, if undetected, may affect package permeability, drug delivery performance, or the adequacy of the seal between the container and the closure. Variation in any physical parameter is considered important if it can affect the quality of a dosage form.

b. Chemical Composition

The chemical composition of the materials of construction may affect the safety of a packaging component. New materials[14] may result in new substances being extracted into the dosage form or a change in the amount of known extractables. Chemical composition may also affect the compatibility, functional characteristics or protective properties of packaging components by changing rheological or other physical properties (e.g., elasticity, resistance to solvents, or gas permeability).

A composition change may occur as a result of a change in formulation or in a processing aid (e.g., using a different mold release agent) or through the use of a new supplier of a raw material. A change in the supplier of a polymeric material or a substance of biological origin is more likely to bring with it an unexpected composition change than a change in the supplier of a pure chemical compound, because polymeric and natural materials are often complex mixtures. A composition change may also occur with a change in the manufacturing process, such as the use of different operating conditions (e.g., a significantly different curing temperature), different equipment, or both.

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[14] These are substances not previously determined to be safe by extraction/toxicological evaluation studies (e.g., the USP Biological Reactivity Tests or another appropriate method conducted on the packaging component as part of the qualifying process).