

Center for Drugs and Biologics
Food and Drug Administration
Department of Health and Human Services

**GUIDELINE FOR SUBMITTING DOCUMENTATION
FOR PACKAGE FOR FAN DIES AID BIOLOGICS**

February 1987

TABLE OF CONTENTS

I. INTRODUCTION.....	3
A. Purpose.....	3
B. General Remarks.....	3
II. CONTAINER CLOSURES Aims MATERIALS CF FABRICATION.....	3
A. Container Types.....	3
1. Parenteral Containers.....	4
a. Glass.....	4
b. Plastic.....	4
2. Nonparenteral Containers.....	4
a. Glass.....	4
b. Plastic.....	4
c. Metal.....	5
3. Pressurized Containers.....	5
4. Bulk Containers for Active ingredient and Drug product.....	5
B. Closure T Types.....	6
1. Caps.....	6
a. Tamper-resistant.....	6
b. Child-resistant.....	6
2. Liners.....	6
3. Innerseals.....	7
4. Elastomers.....	7
5. Aerosols.....	7
6. Miscellaneous.....	7
III. SUITABILITY OF PACKAGE COMPONENTS FOR INTENDED USE.....	8
A. Physical, Chemical, and Biological Characteristics.....	8
B. Specifications and Tests.....	8
C. Stability and Compatibility Considerations.....	9
D. Adhesives and Inks.....	9
IV. INVESTIGATIONAL NEW DRUG APPLICATIONS.....	9
A. Phases 1 and 2.....	9
B. Phase 3.....	10
V. NEW DRUG, ABBREVIATED NEW DRUG, AND PRODUCT LICENSE APPLICATIONS.....	10
A. Original Submissions.....	10
B. Changes in Packaging.....	10
1. Type of Packaging.....	10
2. Closures and/or Liners.....	10
3. Components of Plastics.....	11
4. Sources-Suppliers and/or Fabricators.....	11
5. New Packaging Facility.....	11
6. Interchangeability of Container Materials.....	11
VI. SUBMISSION OF PACKAGING INFORMATION AND DATA.....	12
A. Format.....	12
B. Sponsor/Applicant.....	12
C. Contract Packagers.....	12
BIBLIOGRAPHY.....	13
ADDENDUM.....	14

GUIDELINE FOR SUBMITTING DOCUMENTATION FOR PACKAGING FOR HUMAN DRUGS AND BIOLOGICS

I. INTRODUCTION

A. Purpose

This guideline is intended to furnish pharmaceutical manufacturers with criteria for use in the preparation of information on the fabrication and quality of containers and container components, including details of the packaging processes, as required for submission in a New Drug Application (NDA), an abbreviated New Drug Application (ANDA), an Investigational New Drug Application (INDA), and a Biological Product License Application (PLA).

This guideline is issued under 21 CFR 10.90. An applicant (or sponsor) may rely upon the guideline in preparing applications described above or may follow a different approach. When a different approach is chosen, a person is encouraged to discuss the matter in advance with FDA to prevent the expenditure of money and effort on preparing a submission that may later be determined to be unacceptable.

B. General Remarks

The drug package must maintain the standards of identity, strength, quality, and purity of the drug for its intended shelf life.

The application should contain full information about the containers/closures and materials of fabrication, including details of the packaging processes. This information may be submitted by authorized reference to a Drug Master File (DMF).

The "United States Pharmacopeia/National Formulary" (USP/NF) contains information and the types of packaging and storage required for drug entities. The compendia cover the requirements for preservation, packaging, and storage for drugs. Descriptions of the various tests and procedures for light transmission, chemical resistance, extractables, etc., are part of the compendia.

II. CONTAINER CLOSURES AND MATERIALS OF FABRICATION

A. Container Types

The container criteria for the material most commonly used for packaging various types of pharmaceutical products are listed below, but they are not to be regarded as all inclusive. Additional information may be necessary for other, more unusual types of packaging material, and some of the criteria may not be appropriate in certain instances. For example, only products known to be light sensitive would require light transmission tests for the container material.

Although this information should be submitted initially, only those tests that adequately characterize the package for its intended use need to be run routinely as release specifications.

1. Parenteral Containers (Ampules, Vials, Bottles, Cartridges, Prefilled bleed Syringes, and Bags)

a. Glass

- (1) Name of manufacturer(s)
- (2) Glass type USP
- (3) Physical description (size, shape)
- (4) Light transmission, USP
- (5) Compatibility, which includes leaching and/or migration tests
- (6) Sampling plan
- (7) Acceptance specifications

b. Plastic

- (1) Name of manufacturer(s)
- (2) Type of plastic
- (3) Composition, method of manufacture of the resin and finished container, plus a full description of analytical controls
- (4) Physical description (size, shape)
- (5) Light transmission, as ion, USP
- (6) Tests, USP
 - (a) Biological
 - (b) Physiochemical
 - (c) Permeation
- (7) Vapor transmission test (if appropriate)
- (8) Toxicity studies not included in USP (See Addendum)
 - (a) Subcutaneous on extracts
 - (b) Cell culture
- (9) Compatibility, which includes leaching and/or migration tests (for large-volume plastic containers refer to 21 CFR 310.509)
- (10) Sampling plan
- (11) Acceptance specifications

2. Nonparenteral Containers (Bottles, Unit-dose, and Tubes)

a. Glass

- (1) Name of manufacturer(s)
- (2) Glass type, USP
- (3) Physical description (size, shape)
- (4) Light transmission, USP
- (5) Containers-permeation, USP
- (6) Description of desiccant, if one is present
- (7) Compatibility which includes leaching and/or migration tests
- (8) Sampling plan
- (9) Acceptance specification

b. Plastic

- (1) Name of manufacturer(s)
- (2) Type of plastic
- (3) Composition, method of manufacture of the resin and finished container, plus a full description of analytical controls

- (4) Physical description (size, shape)
- (5) Light transmission, USP
- (6) Physicochemical tests, USP
- (7) Containers-permeation, USP
- (8) Vapor transmission tests
- (9) Description of desiccant, if one is present
- (10) Compatibility, which includes leaching and/or migration tests
- (11) Sampling plan
- (12) Acceptance specifications

c. Metal

- (1) Name of manufacturer(s)
- (2) Composition of packaging and materials of construction. If adhesives are used, as in laminates, their composition might be included.
- (3) Physical description (size, shape)
- (4) Physicochemical tests
- (5) Compatibility, which includes leaching and/or migration tests
- (6) Sampling plan
- (7) Acceptance specifications

3. Pressurized Containers

- a. Name of manufacturer(s) manufacturer(s)
- b. Complete construction, composition, and description of all anent parts of valve closure and container, including valve actuator and aerosolyzing device
- c. Information to assure adequacy of the valve and actuator for the intended use
- d. Leak-testing controls
- e. Compatibility, which includes leaching and/or migration tests
- f. Sampling plan
- g. Acceptance specifications

4. Bulk Containers for Active ingredient and Drug product

As outlined below, the criteria for bulk containers refer to the packaging system used to ship the active ingredient and the drug product. During the early investigational stages of a drug, it may not be necessary to supply this information. These criteria do not refer to the temporary (short-term) packaging used during the manufacturing process. See section V.A. for exceptions permitted for Investigational New Drugs.

- a. Type (fiber, aluminum, etc.)
- b. Type 1 liner (if used)
- c. Moisture barrier studies
- d. Compatibility, which includes leaching and/or migration tests
- e. Description of desiccant, if one is present
- f. Sampling plan
- g. Acceptance specifications

B. Closure T Types

A suitable closure is an essential part of the container/ closure system required to maintain the integrity of a drug product and to ensure its stability, safety, and effectiveness. The components for the closure and the closure design should be selected with due consideration given to drug compatibility and to all factors related to drug preservation and use.

Information to be supplied for closures should be similar to that for containers as outlined under Section II.A. of this guideline,

1. Caps

Caps of various types, such as screw-on, threaded, lug, crimp-on (crown), press-on (snap) and roll-on, should include a liner/contact surface that is compatible with the drug product and capable of providing a tight seal. The closure system should be described in detail and acceptance tests and specifications provided. Such studies as surface/drug compatibility and vapor permeation, including torque, should also be included.

a. Tamper-resistant

Under 21 CFR 211.132, Tamper-resistant packaging requirements for over-the-counter human drug products most over-the-counter (OTC) products must be packaged in a tamper-resistant container. If any part of the tamper-resistant system is in contact with the drug, or potentially could be in contact with the drug, the information suggested in this guideline should be submitted for that closure system.

b. Child-resistant

Under the provisions of the Poison Prevention Packaging Act of 1970 (16 CFR Part 1700), some drugs are required to be in containers with "Special Packaging" as defined at 21 CFR 310.3(1).

This requirement causes no difficulty in the case of a new drug, because the NDA contains a full description of the container and closure, as well as the pertinent suitability and stability studies. Thus, the container characteristics and tests and specifications are reviewed in the normal course of the NDA review.

This requirement applies not only to the familiar screw cap, but also to blister packaging. In this case, child-resistant packaging is usually achieved by designing the film characteristics so that the package is resistant to tear or rupture in the hands of a child.

2. Liners

A liner is an important part of a closure system. It should provide an adequate seal, be compatible with the drug product, and not be a source of contamination. Compliance of any liner components with relevant sections of the regulations, particularly those concerning indirect food additives under 21 CFR Parts 174-178, 181, and 182, may serve as supportive information.

3. Innerseals

An innerseal, such as glassine paper glued to the lip of the container may be used. It is obvious that the innerseal seal and its adhesive must meet the same requirements of compatibility as the closure liner.

4. Elastomers

The materials used in the fabrication of elastomeric and rubber closures may be of synthetic or natural origin. Generally, they consist of a complex mixture of many ingredients, including the basic polymer, fillers, accelerators, vulcanizing agents, and pigments.

The properties of such closures are dependent upon the components and the manufacturing and processing procedures. Standardization of components and processing of closures is therefore important.

The closure manufacturer should provide full information describing the components and composition. This information is usually contained in a DMF. The application should contain an appropriate letter from the closure manufacturer authorizing FDA's reference to the specific information (identified by date) related to the product involved. The applicant should also furnish details of closure tests and specifications, any conditioning treatments, cleaning and sterilization procedures, and test data to show safety and drug product/closure compatibility.

5. Aerosols

When drugs are administered by means of an aerosol dosage form, the valve closure system determines the rate and amount of drug delivered. Therefore, the most critical part of an aerosol or pressurized package is the valve mechanism through which the content of the container is released. Information pertaining to the materials of fabrication, specifications, spray characteristics, compatibility, and stability of the product is particularly important. When metered-dose valves are used, full information is also necessary with respect to accuracy and precision of the dose delivered.

For inhalation or oral dose aerosols, complete information about the actuator, including data showing that it can deliver the medication in the proper particle size, is especially significant. Information should also be provided about the dip tube. Because the dip tube is in immediate contact with, both product and propellant, it should be resistant to both physical and chemical attack.

6. Miscellaneous

Applications for dosage forms and drug containers that require unique package component systems should include special information and data in support of the suitability of their usage. Two such components are medicine droppers and intravenous administration sets.

If a medicine dropper is incorporated as an integral part of the drug container or closure, pertinent information on materials of fabrication and on calibration, compatibility, extractables, stability, etc., should be furnished. Similar pertinent information would expedite

the review process when an unattached intravenous administration set or medicine dropper accompanies a drug package.

Finally for any unusual or uncommon closure, sufficient information about the materials of fabrication and about design, performance, and other pertinent categories discussed above should be furnished to demonstrate conclusively the closure's suitability for the intended use.

III. SUITABILITY OF PACKAGE COMPONENTS FOR INTENDED USE

A. Physical, Chemical, and Biological Characteristics

In recent years, there has been an increased use of plastic containers because of the many advantages they offer. However, plastics can also have distinct disadvantages. Ingredients added to the resin to perform a specific function during fabrication, such as plasticizers, lubricants, mold release agents, pigments, stabilizers, antioxidants, and binding or antistatic agents, may be leached from the plastic into the drug product. Certain ingredients of the drug preparation may bind to the plastic or be absorbed by it, and oxidation, degradation, or precipitation of the drug product may occur. It is also possible for a component of the drug product to migrate through the wall of the container, and oxygen, carbon dioxide, or other gases may pass through the plastic into the drug system. The only way to be certain that a plastic substance is suitable for use as a container is to conduct the appropriate tests.

B. Specifications and Tests

The USP/NF includes test procedures for physicochemical tests for the evaluation of the plastics suitable for drug containers. The tests are based on extraction of specified amounts of plastic by water and are needed to characterize or determine the presence of chemical impurities that result from the manufacturing process.

A number of physical and chemical techniques may be used to identify and characterize plastics. Some characteristics that are frequently considered are IR spectrum (ATR), UV, thermal analysis, melt viscosity, molecular weight, molecular weight distribution, polymer linearity, degree of crystallinity, permeability, stiffness, softening temperature, films or sheet thickness, ash, and heavy metals. Additional testing of plastic containers may include the effect of moderate degrees of cold or heat, water vapor and light transmission, and the extent of degradation under exposure to heat and light.

Biological testing should be conducted when appropriate. The USP/NF contains biological test procedures for plastics. In addition to the compendial tests, applicants should also submit the results of any other biological testing of plastic containers and closures, e.g., exposure to cell culture, blood platelets, subchronic mouse toxicity test, and the USP XXI eye irritation studies.

Certain of these tests and specifications are also applicable to elastomeric closures. The USP/NF includes a specific section for testing of elastomeric closures for injectable products. Multiple-entry penetration of vial stoppers is of particular interest. The integrity of the stopper after many entries and withdrawals should be demonstrated by studies that reflect the maximum entries/withdrawals using the lowest strength of the dosage form. In addition to demonstrating stopper integrity, studies

should be conducted and data submitted to demonstrate product integrity after the maximum entries/withdrawals have been made.

Certain parts of 21 CFR (e.g., Part 177) pertaining to food additives also provide useful guidance in the evaluation of plastics as packaging materials. However, packaging that has been found to be safe in contact with food may not necessarily be safe in contact with drugs.

C. Stability and Compatibility Considerations

Samples of a drug that are selected for stability studies should be packaged in the container/closure system in which the drug is to be marketed or distributed. Because a drug may absorb toxic impurities from its container/closure system, or react with or be absorbed by the container/closure system, tests to define and control any of these possible problems should be performed. The leaching studies conducted in accordance with the USP procedure would provide part of these tests. Furthermore, laboratory examination should be conducted, when appropriate, to assure that contamination with microorganisms or foreign matter will not occur through the container or closure.

D. Adhesives and Inks

Some substances, such as cements and lacquers used as label adhesives, are not water-based emulsions. They are usually dissolved in toluene, alcohol, naphtha, benzol, methyl ethyl ketone, or other organic solvents.

When an adhesive of this type is used on plastics or elastomers, the solvent may allow migration of adhesive components into the drug. Appropriate testing should be performed to determine whether either adhesive and ink components migrate through the container. If they do, adequate information to justify the use of the container system in combination with the drug product should be submitted.

For all containers, testing should be conducted on the effectiveness of the adhesive under appropriate challenge conditions (e.g., temperature and humidity).

If direct label imprinting is used on containers, such as on containers of injectable drug products, it is necessary that resistant ink be used so that the imprint having the required information resists the normal handling of the containers during their customary conditions of purchase and use.

IV. INVESTIGATIONAL NEW DRUG APPLICATIONS

A. Phases 1 and 2

The IND should describe the packaging and labeling used for the drug substance and the dosage form, as well as any precautions necessary to protect and preserve the product from the time of manufacture until the time of clinical use.

During the initial stages of the investigational studies, the packaging used should be a type that will assure adequate protection. In the case of bulk containers, all the information listed under II.A.4. may not be available. In these early stages, the IND should also indicate that appropriate stability studies with the appropriate packaging have been initiated. Subsequently, these studies should be expanded to include other types of containers that may be considered suitable for distribution of the drug.

B. Phase 3

When clinical studies advance into Phase 3 involving greater patient population exposure to the drug, additional attention should be focused on the product packaging and the related stability information. The information furnished on the chemical, physical, and biological characteristics of, and the test methods used for, the container, closure, and other component parts of the drug package to assure their suitability should be directed toward fulfilling requirements for the future submission of an NDA or PLA. In order to facilitate the proper review of the NDA/PLA, by the end of Phase 3 the IND should contain complete information pertaining to the packaging of the drug. This information should include the proposed market package for the product and the relevant stability and compatibility data.

V. NEW DRUG, ABBREVIATED NEW DRUG, AND PRODUCT LICENSE APPLICATIONS

A. Original Submissions

Sections II and III describe the type of information that should be provided for drug containers and closures. All applicable information should be submitted in sufficient detail to permit evaluation of the packaging for its intended use.

B. Changes in Packaging

Requests for changes in packaging are made by filing an amendment to all unapproved applications and to approved PLA's. For an approved NDA, request for changes in packaging should be made in accordance with 21 CFR 314.70. Examples of types of changes are as follows:

1. Type of Packaging

Changes could involve substitution of glass for plastic, or vice versa, addition of strip, blister, or unit-dose packaging, or a change from one plastic to another.

When the change is from one polyethylene (PE) type to another for solid, oral-dosage forms, the applicant may comply with tests and specifications in the USP chapter dealing with PE. An independent protocol of tests and specifications may also be submitted for review and approval if a firm desires to use requirements other than those in the USP.

The information submitted should include a full description of the new package, the components and sources. The applicable tests as detailed in this guideline should also be followed.

In all cases, the data should show that the change does not or compromise the integrity of the drug product.

2. Closures and/or Liners

When a change is made, a complete description of the closure system, compatibility studies, and all applicable tests and results as appropriate to the drug substance and dosage form should be submitted.

3. Components of Plastics

Complete information on tests, specifications, and results for the components and on compatibility of the plastic with the drug should be submitted. The applicable tests detailed in this guideline should also be included.

4. Sources-Suppliers and/or Fabricators

The identity of the source and a description of the for formulation(s), process(es), and controls(s) should be submitted for review. This information may be submitted directly to the application(s) or by authorized reference to the DMF(s).

5. New Packaging Facility

A full description of the packaging process and controls should be furnished directly or by authorized reference to a DMF.

6. Interchangeability of Container Materials

If there is a need for interchangeability of container/closure materials for the drug product from one composition or supplier of a generic resin to another and the change is based upon a showing of equivalency with the approved system under a protocol approved in the application or published in an official compendium, this change may be made and reported in the annual report. It must be clear whether the proposed protocol for showing equivalency will or will not be used for future generic resin changes. Before this change may be placed into effect, three conditions must be met:

- a. The container and closure system together with its protocol of testing must be the subject of an approved application or supplement;
- b. The proposed change in the system must have been studied in accordance with the approved protocol (in the NDA or USP) and have been found not to alter any of the important physicochemical parameters that describe the system; and
- c. The stability studies that were originally performed to establish the expiration date for the particular drug product nut have been expanded to include the alternative container in order to assure that the identity, strength, quality, and purity of the drug product will be maintained throughout the expiration period. If the desired interchangeability is performed under any of the following conditions, then prior approval of a supplement is required as described in 21 CFR 314.70(b)(2)(vii)
 - (1) For polyethylene tests and specifications other than those in the current USP or if different from an approved protocol.
 - (2) For changes from glass to plastic or from one type of plastic to another (e.g., polyethylene to polyvinyl chloride).

VI. SUBMISSION OF PACKAGING INFORMATION AND DATA

A. Format

The descriptive information necessary for various types of packaging has been indicated in Sections III and IV of this guideline. The outline below indicates the format in which to submit information about packaging components: ampules, vials, cartridges, pre-filled syringes, large-volume bottles/bags, bottles, unit-doses, tubes, pressurized containers, bulk-drug containers, fillers, closures, liners, blister-packaging components, and adhesives and inks.

1. Name of manufacturer(s)
2. Description of packaging components and processes
3. Sampling plan
4. Acceptance specifications
5. Test methodology

B. Sponsor/Applicant

In compliance with pertinent regulations, written procedures detailing the identification, handling, sampling, testing, and approval or rejection of components of drug product containers and closures should be included in submissions. The entire packaging operation and relevant in-process controls should be described.

C. Contract Packagers

When contract packagers are used, the supporting information, which may be referenced to a DMF, should be as detailed as that required of the sponsor/applicant as stated above.

BIBLIOGRAPHY

1. "Guidelines: Manufacturing and Controls for IND's and NDA's," FDA Papers. June 1971, FDA 72-3013, U.S. Government Printing Office, Washington, D.C., 1972-482-082/5.
2. The "United States Pharmacopeia, Twenty-first Revision/The National Formulary, Sixteenth Edition," United States Pharmacopeial Convention, Inc., Rockville, Maryland, 1985.
3. Federal Food Drug, and Cosmetic Act, as Amended, and Related Laws; HHS Publication No. (FDA) 86-1051, U.S. Government Printing Office, Washington, D.C, 1986.
4. Title 21, Code of Federal Regulations, The Office of the Federal Register, National Archives and Records Service, General Services Administration, U.S. Government Printing Office. Washington, D.C.
5. Lachman, L., H. A. Lieberman, and J.L. Kanig, "The Theory and Practice of Industrial Pharmacy," 2nd Ed., Lea & Febiger, Philadelphia, 1976.
6. Hanlon, F.J., "Handbook of Package Engineering," McGraw-Hill Book Company, New York, 1971.

ADDENDUM

Biological Testing of Plastic Containers for Parenteral Products

Ever since the inception of the USP Biological Test-Plastics, reviewers within the Center for Drugs and Biologics (CDB) have believed that plastics used for containers of parenteral drugs must qualify as Class IV, Class V, or Class VI.

Past sponsors who have sought approval from CDB for either clinical investigation or marketing of parenteral drugs in plastic containers have gone beyond the requirements of the USP and provided additional safety information. Usually, these sponsors have chosen either one of two approaches in their effort to expand the biologic testing of the plastic under consideration. Approaches that may be used are as follows:

1. Cell-culture studies - The following may be helpful references to who are unfamiliar with what may be a difficult technique:

- (a) Guess, W.L., et al., "Agar Diffusion Method of Toxicity Screening of Plastics on Cultured Cell Monolayers," Journal of Pharmaceutical Sciences, 54:1945, 1965.
- (b) Wilsnack, RE., "Human Cell Culture Toxicity Testing of Medical Devices and Correlation to Animal Tests, Biomaterials, Medical Devices, Artificial Organs, 1:543, 1973.

The second reference uses human WI-38 cells, but one consulting laboratory finds little difference in the sensitivity of these cells and the more readily available strain L929 mouse cells.

2. Mouse subchronic systemic and other biological tests

The test plastic is extracted with 0.9% sodium chloride solution in the same ratio of surface area to solvent and under the same temperature conditions as used in the official USP procedure. Three groups of 10 mice are used for the test material and three groups for the blank. The extracts or blanks are administered daily intravenously at a dose of 50 mL/kg of body weight and at a rate of 3 ml/min for a total of 9 daily injections. Twenty-four hours after the last injection, the mice in one group are weighed and sacrificed. A second group is sacrificed after 1 month and the third group is sacrificed after 3 months. The following organs are examined for gross pathology: heart, lungs, liver, spleen, kidneys, and gonads. The major organs of the animals are placed in fixative and saved for future histological preparation. The effect should not differ from that produced by a blank. A further test to supplement the mouse subchronic systemic test is the procedure for eye irritation included under Containers for Ophthalmics-Plastic in USP XXI. Supplementary testing for anticoagulant solutions in plastic containers may include additional tests such as erythrocyte and platelet survival studies. A number of in vitro tests may also be required, such as platelet function, platelet and red cell morphology, and complement activation studies.