
PHARMACEUTICAL SCIENCES

GUIDANCE ON THE PACKAGING OF TEST BATCHES

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PURPOSE

- To provide information concerning the processing, packaging and labeling of test batches for Abbreviated New Drug Applications (ANDA), Abbreviated Antibiotic Applications (AADA) and Supplements.

BACKGROUND

- ANDAs and AADAs are usually approved based on data from a single test batch. It is critical that all testing be conducted on samples that represent the entire batch and mimic the product which will be marketed post-approval. Therefore, the November 8, 1991 and August 4, 1993 letters from the Office of Generic Drugs to industry stated that, for solid oral dosage forms, the entire test batch should be processed and packaged. Since the issuance of these letters, industry has periodically requested additional clarification and guidance on issues relating to the packaging of the test batch for all dosage forms.

POLICY AND PROCEDURE

- The policies and procedures described below apply only to test batches manufactured for ANDAs, AADAs and supplements to these applications as submitted to the Office of Generic Drugs. Test batches prepared for New Drug Applications, which are reviewed by the Offices of Drug Evaluation (ODE) I or II, are not covered by this Guide. Also, test batches prepared for Investigational New Drug applications are not covered by this Guide.
 - **Definitions**
 1. **Test Batch** - A batch of finished drug product manufactured according to cGMP regulations in support of an ANDA or AADA. See MAPPs 5223.3 and 5223.1 (formerly Office of Generic Drugs Policy and
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Procedure Guides #22-90 and #35-92) and 21 CFR 210.3 (b)(2).

2. Bioequivalence Batch - A test batch, portions of which have been designated for bioequivalence studies.
3. Uniform - Having the same physical and chemical properties, within specified limits, throughout the batch.
4. Representative sample - A sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled. [21 CFR 210.3 (b)(21)].
5. Group labeling - Identification applied to a group of filled product containers that are set aside and held in unlabeled condition for future labeling operations. [21 CFR 211.130 (b), as revised August 3, 1993].
6. Compounded bulk product - The finished blend of active ingredient combined with most, if not all, of the excipients.
7. Processed Material - Unpackaged finished drug product.

- **General Policies**

1. Except as noted below, the entire test batch for all dosage forms should be completely processed and packaged.
2. To demonstrate that the test batch is uniform, the applicant should provide data obtained from in-process controls at key manufacturing steps.
3. The applicant should always use production filling and packaging equipment for the test batch.
4. The applicant may fill multiple sizes of the proposed market containers from the same test batch. An attempt should be made to fill the same number of containers for each container size. A storage drum is not considered a market container. A bulk container intended for sale to repackagers is considered a market container.
5. The Packaging and Labeling Sections of the batch record should contain complete records for the packaging and labeling operations, including drug product and label reconciliation.
6. The Packaging Section of the batch record should include a summary

table of packaging information describing the container/closure system, the total number of containers packaged and the quantity disbursed, and the destination of all disbursements of the packaged product.

7. Packaged product selected for testing should be representative of the batch.
8. Test batches should be labeled in accordance with the current requirements of Title 21 CFR and the United States Pharmacopeia.

- **Demonstration of Uniformity of the Test Batch**

All batches are expected to be uniform within normal process variation. Process validation studies are conducted prior to the marketing of a drug product to assure that production processes are controlled. The test batch is manufactured prior to validation, yet it is the basis on which an application is approved.

It is essential, therefore, to assure that the test batch is uniform. In-process tests for uniformity should be conducted throughout the entire production process, e.g., at commencement or completion of significant phases (21 CFR 211.110). These tests should be designed to detect potential in-process anomalies.

1. The following test samples should be taken:
 - a. samples of compounded bulk product (e.g., granulation, blend, solution, etc.) obtained from the mixing vessel (including samples taken from "dead spots"),
 - b. samples of compounded bulk product obtained from storage drums (samples should not be composites),
 - c. samples of processed material collected either from throughout the entire production run or, alternately, from the beginning, middle and end of the production operation.
2. Testing should include, for example, assay and physical parameters such as sieve analysis; density and viscosity for creams; unit weight, hardness, thickness, friability, dissolution and assay for tablets; and dissolution, weight variation and assay for capsules.

- **Selecting Packaged Samples of the Test Batch**

The packaged product should be used for initial testing, reserve samples at the site of manufacture, bioequivalence studies, reserve samples at the site of the bioequivalence study and stability studies. As an example, the number of containers which might need to be sampled in support of an application for a

solid oral dosage form may be as follows:

Minimum Number of bottles needed for Solid Oral Dosage Forms

	Initial testing	Chemistry		Bio	
		Reserves	Bioequivalence	Reserves	Stability
100 s	1	2	2	5	18
500 s	1	2	2	5	(18 optional)
1000 s	1	1	-	-	6

The samples should be systematically selected at intervals from the packaging line. For example, if one needs 28 bottles of 100 tablets from a test batch of 100,000 units, then one should select every 35th bottle. If the packaged product is not sampled from the packaging line, then a random sampling procedure should be used. The procedure should be documented and shown to be appropriate for the drug product.

● **Packaging of the Test Batch**

Normally, the Office will issue a Refuse to File letter for an abbreviated application that fails to provide data supporting complete packaging of the test batch. The following examples elaborate on that policy. Dosage forms not specifically described below will be considered on an individual basis.

1. The following dosage forms should be **fully packaged**:

a. Sterile products

Per the August 4, 1993 letter from the Office of Generic Drugs to industry (Section "5. Parenteral Scale-up Requirements"), the test batch should be fully packaged.

b. Semi-solids (suspensions, lotions, ointments, creams and gels)

Semi-solid products are not considered to be fully processed until they are packaged.

c. Metered-dose Inhalation products

The test batch should be at least 10 percent of the size of the proposed production batch and provide a minimum of 5,000 containers. The minimum batch size is determined by the number of containers produced, not by the total volume or dosage unit quantity, and it should be completely packaged.

2. **Partial packaging** of tablets and capsules will be accepted **without a previously approved protocol** if the packaging operation meets the

following criteria:

- a. The minimum amount to be packaged is 100,000 units.
- b. In-process data are provided which demonstrate that the batch is uniform.
- c. A sampling protocol is provided which demonstrates that samples are taken in a representative manner. For capsules or uncoated tablets, samples are taken for packaging from throughout the batch at measured intervals (such as the weight check samples). If coated tablets are sufficiently mixed during the coating operation, a randomized sample of 100,000 units may be taken from the coating machine for packaging (i.e., sampled without the use of measured intervals).
- d. A statement is provided to the effect that the manufacturing and packaging was performed in compliance with this section of the Policy and Procedure Guide.

3. **Partial packaging** for the following products will be considered if, before the firm submits the application, the Office approves a "packaging protocol."

a. Tablets and Capsules

A protocol for partial packaging should be submitted if all of the criteria listed under the preceding item 2. above are not met.

b. Non-Sterile Liquids

For liquids, the total amount of bulk product packaged should be, at a minimum, 10 percent of the proposed production batch, but not less than the minimum number of samples that will meet the needs for test samples and reserve samples described in Section D.

c. Transdermal Patches

The test batch size should be at least one tenth of the proposed commercial production batch or 25,000 units for each strength, whichever is greater. OGD will consider, on a case-by-case basis, protocols to package less than the entire test batch.

- **Protocol for the Partial Packaging of the Test Batch**

A protocol should be submitted as a control document directed to the Acting Director, OGD as described in the April 1994 Office of Generic Drugs Industry Letter. The protocol should be capable of demonstrating that the test batch is chemically, physically and microbiologically uniform. Adequate controls should be proposed.

The requestor should provide the following information in the opening statement of the letter:

1. Indicate whether the request is a general question or applies specifically to an individual or class of applications and provide the application numbers, as appropriate.
2. Indicate the nature of the request, and provide a reference to the appropriate sections of relevant guidelines, policies or regulations in question, clearly stating the deviation.
3. Indicate the applicable dosage forms and strengths.

The protocol should provide the following:

1. a description of the dosage form and its properties, including any characteristics that may be affected by environmental factors such as heat, light, humidity and oxygen,
2. a description of the container/closure system and packaging and labeling operations, and
3. a description of the sampling plan and analytical methodology.

● **Labeling**

1. The test samples for the bioequivalence study and the reserve samples at the site of the bioequivalence study should be labeled in accordance with 21 CFR 211 and 312.
2. Packaged product which is not intended for immediate use may be group labeled.
3. For certain products packaged in plastic (e.g. inhalation solutions in LDPE), there are concerns regarding permeation of packaging/labeling material components (inks, adhesives, solvents, etc.) through drug product container/closure systems. These packages should be labeled in the same manner in which they are to be labeled for marketing. For example, if the bottles are to be labeled with video ink or ink jet, the process should be the same as that intended for the proposed market

container.

REFERENCES

- 21 CFR 314 Applications for FDA Approval to Market a New Drug or an Antibiotic Drug:
 - 314.50 Content and Format of an Application
 - (d)1 Chemistry, manufacturing, and controls section.
 - (ii) Drug Product.
 - 314.94 Abbreviated application (requirements)
 - 21 CFR 211 Subpart G cGMPs
 - 211.122 Materials examination and usage criteria
 - 211.125 Labeling issuance
 - 211.130 Packaging and labeling operations
 - 211.130(b) (revised August 3, 1993)
 - November 8, 1991, Office of Generic Drugs Industry letter; Section "7. Completion of Tableting and Packaging."
 - August 4, 1993, Office of Generic Drugs Industry letter; Section "4. Minimum Packaging requirements for the Test Batch" and Section "5. Parenteral Scale-up Requirements."
 - Guideline For Submitting Documentation For The Manufacture of and Controls for Drug Products, Section on Drug Product (ANDAs and NDAs), Methods of Manufacturing and Packaging, Production Operations (Section II. E. 1 Feb 1987).
 - April 8, 1994, Office of Generic Drugs Industry letter; Section "4. Minimum Batch Size for Transdermal Products" and Section "8. Requests for Deviation from OGD Policy."
 - Guide to Inspections of Oral Solid Dosage Forms Pre/Post Approval Issues For Development and Validation, January 1994.
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EFFECTIVE DATE

This guide is effective upon date of publication.