Guidance for Industry

Variations in Drug Products that May Be Included in a Single ANDA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998

OGD 2

Guidance for Industry

Variations in Drug Products that May Be Included in a Single ANDA

Comments and suggestions regarding this document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the guidance. All comments should be identified with the docket number provided at the beginning of the notice. Submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Parklawn Dr., rm. 1061, Rockville, MD 20852.

After the comment period closes, comments should be provided in writing to the Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857.

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
The Drug Information Branch, HFD-210
5600 Fishers Lane, Rockville, MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998
OGD 2

TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY[1]

Variations in Drug Products that May Be Included in a Single Abbreviated New Drug Application

I. INTRODUCTION

This guidance is intended to provide information to applicants on certain specific variations of a drug product that should be included in a single abbreviated new drug application (ANDA) and describe the general factors to be considered when determining whether single or multiple ANDAs should be submitted.

Prior to October 1, 1990, applicants were to submit separate ANDAs for each drug dosage form and for each variation (e.g., strength or color) within a dosage form. Historically, applications were separated for ease of review and postapproval tracking. On October 1, 1990, the Office of Generic Drugs (OGD) issued the Interim Policy and Procedure Guide (PPG) 20-90. This guide permitted certain variations of solid oral dosage forms and injectables to be submitted within a single abbreviated application. On June 7, 1995, PPG 20-90 was amended to allow certain variations to be submitted as supplements.

This guidance incorporates the policies and procedures in PPG 20-90, clarifies the practice of including variations of products in a single application, and reduces the burden on industry for submitting and maintaining separate applications for certain variations of the same drug product.

II. GENERAL CONSIDERATIONS

To minimize disruption of the review of pending applications, OGD recommends that applications that have already been submitted but not approved be maintained as submitted. To aid in administrative tracking, OGD also suggests that applications submitted before December 31, 1998, continue to follow the policies described in OGD PPG 20-90. For applications submitted after December 31, 1998, OGD recommends that applicants refer to this guidance to determine whether one or more ANDAs should be submitted for variations of a specific drug product dosage form.

A. Reference Listed Drugs (RLDs)

---

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on variations in drug products that may be included in a single abbreviated application. 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 statue, regulations, or both.

To determine which variations of a product should be included in a single abbreviated application, the initial consideration is whether there are separate NDAs as reference listed drugs (RLDs) or whether there is a single NDA as a RLD. (For example, when the same drug product is used for two separate indications, that product might have two separate NDAs as RLDs.) Generally, when there is a separate NDA as a reference listed drug for a specific drug product there should be a separate abbreviated application for that NDA. However, as described in sections B through G of this guidance, this will not always be the case.

B. Multiple Bioequivalence Studies

Separate ANDAs should be submitted when, because of certain variations in the drug product (e.g., formulations, shapes), an in vivo bioequivalence study cannot be waived (21 CFR 320). Examples of this situation include:

- Formulation Differences. Two products should not be included in the same application if two strengths of a capsule have differences in formulation or if there are questions about absorption of the products so that an in vivo bioequivalence waiver would not be granted for the lower strength, even if a bioequivalence study was performed on the higher strength (21 CFR 320.22(d)(2)).

- Multiple combinations of strengths, shapes, and colors for oral solids. Where there are such multiple combinations, separate in vivo bioequivalence studies should be performed and separate applications should be submitted (21 CFR 320.22(d)(4)).

More specific guidance on this can be found in Section III, Specific Dosage Forms.

There are instances when a single ANDA can be submitted even if the application includes more than one bioequivalence study. For example, if there are five strengths of a product and there is acceptable proportionality of inactive ingredients, but the Division of Bioequivalence (DBE) has suggested separate bioequivalence studies on the lowest and highest strengths, all five strengths may be included in the same application. In this case, the studies are not related to a difference in formulation but have been recommended to ensure the equivalence of a product across a wide range of strengths.

C. Different Excipients

Any product variations because of differences in excipients (e.g., absorption enhancers or hydrophobic agents) or other changes in formulation that may significantly affect absorption of the active drug ingredient or active moiety should be submitted in separate applications. This would include products with differences in excipients where separate

bioequivalence studies are recommended.

Topical products with differences in excipients where separate in vivo demonstration of bioequivalence is recommended should be submitted in separate applications.

D. Different Dosage Forms

Different dosage forms should be submitted in separate applications. (See the FDA publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*.)

E. Pharmacy Bulk Packages

Pharmacy bulk packages should always be submitted as separate applications. Strengths or fill volumes for pharmacy bulk packages that can share a single application should be determined based on the RLD.

F. Different Strengths or Concentrations

Different strengths or concentrations of a drug product or combination product, if they are the same dosage form, intended for the same route of administration, and have the same indications, should be submitted in one original application when their qualitative composition is the same. (See Section IV for additional guidance.)

G. Different Container Sizes and Configurations

Except for pharmacy bulk packages, products utilizing different container sizes, configurations, and materials (e.g., glass or plastic) of one finished pharmaceutical product intended to be used for the same route of administration and for the same indications (consistent with the RLD) may usually be included in a single application, within certain limitations.

In general, separate applications should be submitted for special packaging systems. In this context, ***special packaging*** may describe novel or technologically new container closure systems or packaging to serve the special needs of the intended population. A major consideration in deciding if single or multiple ANDAs would be recommended is whether significantly different manufacturing processes for which there is little experience would be used in the special packaging. Because of the range of possibilities that special packaging provides, such applications will generally be treated on a case-by-case basis. If applicants are considering novel or nontraditional processes for packaging, it is suggested that the specific situations should be discussed with OGD prior to submitting applications.

Different packaging formats in which the drug delivery device is integral to the use of the product usually should be submitted as separate applications. In this case the

manufacturing process for the packaging format may be a consideration. Examples include syringes, aerosol or pressurized (powered) dispensers versus manually operated pump dispensers, and product-loaded swabs versus applicator bottles or separate solutions and applicators. Unit and bulk packed product-loaded swabs, however, could be included in a single application.

III. SPECIFIC DOSAGE FORMS

The considerations for more prevalent specific dosage forms are detailed below. For dosage forms not specifically covered, please refer to Section II - General Considerations. The recommendations in Section III are intended to provide the applicant with sufficient information to determine whether separate applications should be submitted for other dosage forms. If there are still questions, the OGD should be contacted for assistance.

A. Solid Oral Dosage Forms

The chart below is a restatement of the information set forth in PPG 20-90. Applicants should limit the number of variations in a single application. Limiting the variations makes the review process simpler and allows more accurate tracking of postapproval changes. Only the following combinations of strengths, color, and shapes should be included in a single application.

SOLID ORAL DOSAGE FORMS

One strength One color One shape	=	Single application
One strength One color Multiple shapes	=	Single application
One strength Multiple colors One shape	=	Single application
Multiple strengths One color One shape	=	Single application
Multiple shapes	=	Only one color per shape per strength should be submitted in a single application. Different combinations should be submitted in separate

applications.

B. Parenteral Products

Each application for a parenteral product should be limited to a common formulation. When more than one strength of a product exists, some small formulation differences may be included in a single application. A common example of such a difference is the amount of inactive ingredient needed to produce tonicity. Preserved and nonpreserved formulations, however, are considered to be different formulations, and separate applications would be recommended.

Varying fill volumes (e.g., 2, 5, and 20 mL vial sizes) may be included in the same application, but drug products with different container materials or packaging systems should be submitted as separate applications.

PARENTERAL SOLUTIONS AND SUSPENSIONS

One formulation One strength	=	Single application
One formulation Multiple strengths	=	Single application
Multiple formulations (e.g., preserved or unpreserved) One strength	=	Multiple applications*
One formulation One strength Multiple fill sizes	=	Single application**

One formulation One strength One or multiple fill sizes, Multiple packaging types, or container materials	=	Multiple applications, depending on the number of package types and/or container materials used

*Some small formulation differences, such as the amount of an inactive ingredient needed to maintain tonicity, may be included in a single application with different strengths. Additionally, each application should be limited to a single dosage form.

** Except Pharmacy bulk packages. Pharmacy bulk packages should always be submitted as separate applications.

PARENTERAL STERILE SOLIDS

One formulation One or multiple fill quantities Single container/closure system	=	Single application
One formulation One or multiple fill quantities Multiple container/closure systems	=	Multiple applications
Multiple formulations	=	Multiple applications

C. Transdermal Products

The method of manufacture of a transdermal product usually determines whether one or more applications would be recommended. For example, if the active ingredient is contained in the patch adhesive, the same application should not contain submission data for a product where the active ingredient is contained in a reservoir. Transdermal systems of the same size which release different amounts of the active ingredient through a membrane should be submitted in separate ANDAs, because each strength uses different manufacturing procedures and controls. However, transdermal products in which the active ingredient is in the same component of the patch, but product strength depends upon the patch size, should be in a single application.