Guidance for Industry

Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs

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

December 2000

Office of Generic Drugs

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This guidance represents the Food and Drug Administration's current thinking on this topic. 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 statutes and regulations.

I. INTRODUCTION

This guidance is intended to describe the Office of Generic Drugs' (OGD) policy on the use of alternate sources of the active pharmaceutical ingredients (API) in unapproved abbreviated new drug applications (ANDAs). The guidance describes the circumstances under which an alternate source can be used. This guidance is intended to decrease the regulatory burden on industry and provide a more consistent approach to pre- and postapproval changes in API sources.

This guidance replaces the OGD memorandum dated July 26, 1996, titled, *Substitution of an Alternate Source of the New Drug Substance in Unapproved Abbreviated Applications.*

II. BACKGROUND

In the early 1990s, if an ANDA was approvable, except for an unsatisfactory current good manufacturing practice (CGMP) inspection for the primary API supplier, the application would not be approved until the CGMP issues were resolved. In some cases, application approval was delayed because API suppliers remained unacceptable for months or even years. In other cases, a supplier would close a facility thereby

[1] This guidance has been prepared by the Office of Generic Drugs (OGD) in the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

precluding approval. To qualify an acceptable alternate API source for use in the bioequivalence or test batch, a new batch (and depending on the dosage form, a new in vivo bioequivalence study) based on the alternate source was requested prior to approval.

III. WHEN CAN AN ALTERNATE SOURCE BE SUBSTITUTED?

An ANDA applicant can propose an alternate source for the API if the applicant can assure the Agency that the specifications and test data are essentially the same as those of the API originally used in the bioequivalence or test batch. Generally, a new in vivo bioequivalence study will not be needed using the alternate source. However, applicants should provide comparative dissolution data depending on the dosage form of the proposed product. This policy conforms to existing policy regarding postapproval changes providing for alternate sources of API.

To substitute an alternative source for the API, the following circumstances should exist:

1. The original API source is not being withdrawn due to deficiencies specifically relating to that API, such as:

    - Lack of adequate controls
    - Evidence of adulteration
    - Evidence of falsification of data in the application or identified in the pre-approval inspection

    If any of these situations apply, a new acceptable bioequivalence (test) batch, an *in vivo* bioequivalence study (if dictated by the dosage form), and comparative dissolution data for all strengths (based on the dosage form) will be needed to support the alternate source of the API (21 CFR 314.50(d)(1)(i) and (ii)).

2. The previous bioequivalence (test) batches and bioequivalence studies were acceptable except for the CGMP issues that were specific to the original API.

3. The specifications of the alternate source API are essentially the same as the original source API.

IV. WHAT IS THE PROCEDURE FOR CHANGING THE SUPPLIER?

Applicants should submit an amendment to their pending application requesting the withdrawal of the primary API supplier with the supporting information to add the new supplier just as is expected for any supplier of an API. The amendment should include the dissolution data, waiver request, or other data necessary (§§ 314.50(d)(1) and

314.94(a)(7)). Any potential concerns about falsification of data related to the original source that might affect the application will be evaluated by the reviewer. All specifications and data for the new source will be reviewed including comparative dissolution data. The Agency will also perform an establishment inspection for the new source.