
Guidance for Industry Residual Solvents in Drug Products Marketed in the United States

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2008**

CMC

Guidance for Industry

Residual Solvents in Drug Products Marketed in the United States

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**U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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Guidance for Industry¹
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I. INTRODUCTION

This guidance is intended to assist manufacturers in responding to the issuance of a new USP test requirement² for the control of residual solvents in drug products marketed in the United States. Specifically, this guidance makes recommendations on the following:

1. How holders of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for compendial drug products should report changes in chemistry, manufacturing, and controls (CMC) specifications to FDA to comply with the USP's General Chapter <467> "Residual Solvents" and 21 CFR 314.70
2. How manufacturers of compendial drug products that are not marketed under an approved NDA or ANDA can comply with the new <467> and the Federal Food, Drug, and Cosmetic Act (the Act)

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND/POLICY

On July 1, 2008, the United States Pharmacopeia (USP) implemented a new test requirement for the control of residual solvents in drug products marketed in the United States. The new test requirement, General Chapter <467> "Residual Solvents," will replace the current USP General Chapter <467> "Organic Volatile Impurities." The effective date of this change is July 1, 2008.

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

² United States Pharmacopeia (USP); General Chapter <467> "Residual Solvents"

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Beginning July 1, 2008, FDA will require³ that U.S. marketed drug products with an official USP monograph meet the residual solvents requirements in the revised General Chapter <467>.

III. RECOMMENDATIONS

FDA makes the following recommendations concerning implementation of the new USP testing requirement General Chapter <467> “Residual Solvents.”

A. Compendial Drug Products Approved Under an NDA or ANDA

- Beginning July 1, 2008, FDA will require that U.S. marketed drug products with an official USP monograph (compendial drug products) meet the residual solvents requirements in the new USP General Chapter <467>.

Current General Chapter <467> allows direct testing of finished drug products for residual solvents to determine compliance. However, new General Chapter <467> provides options for testing the active pharmaceutical ingredient and excipient components of the finished drug product for residual solvents; it also provides for using these test results to determine whether the finished drug product complies with the test limits. If the test limits are met, finished product testing is unnecessary.

- FDA will accept the use of analytical procedures other than those included in the revised General Chapter <467>.

The USP General Notices section on “Tests and Assays – Residual Solvents” references the use of “suitable methods” other than the specific analytical methods included in General Chapter <467>. FDA will accept the use of such other analytical procedures as referenced in 21 CFR 314.50(d) provided that all such procedures are properly described and validated and their suitability verified under actual conditions of use as described in the current good manufacturing practices (CGMPs) regulations in 21 CFR 211.165(e) and 211.194(a)(2).

For compendial drug products approved under an NDA or ANDA, changes made to the specifications in the approved application regarding the revised General Chapter <467> should be in accordance with applicable regulations described in 21 CFR 314.70 and the recommendations in the guidance for industry on *Changes to an Approved NDA or ANDA*.

FDA expects that in most cases, an annual report can be used to report changes such as adding a test to a finished product specification or adding an alternative analytical procedure to a specification to comply with the USP. In these cases, the annual report must contain the information described in 21 CFR 314.70(d)(3). However, detailed data from technical studies and tests can be summarized rather than submitted in full. A copy of the full, documented data as described in 21 CFR 210 and 211 should be kept available at the manufacturing site for the Agency to review upon request during a site inspection.

³ The Federal Food, Drug, and Cosmetic Act, Section 501(b).

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- Applicants can submit an amendment to their NDA or ANDA to document any changes made to implement the revised General Chapter <467> if the drug products are the subject of an official USP monograph and the applicants have already submitted NDAs or ANDAs to the Agency for approval.

The amendment should be submitted as soon as possible. Similarly, this same information should be included in all new NDAs and ANDAs submitted for compendial drug products.

B. Compendial Drug Products Not Approved Under an NDA or ANDA

Marketed compendial drug products not approved under an NDA or ANDA (e.g., over-the-counter (OTC) drug products marketed under an FDA OTC monograph) are also subject to the provisions of the Act, the revised General Chapter <467>, and the CGMP documentation requirements described in 21 CFR 210 and 211. Analytical procedures other than those in the revised General Chapter <467> can be used, provided that all such procedures are properly described and validated and their suitability verified under actual conditions of use as described in 21 CFR 211.165(e) and 211.194(a)(2).

C. Non-compendial NDA or ANDA Drug Products

The revised General Chapter <467> does not apply to non-compendial drug products. However, FDA recommends that NDA and ANDA applicants for non-compendial drug products control and limit residual solvents as described in guidance for industry *Q3C Impurities: Residual Solvents*. Applicants who have not included control and limit of residual solvents information in their NDA or ANDA, per CFR 314.50(d), should amend their pending applications as soon as possible.