Guidance for Industry

Residual Solvents in Drug Products Marketed in the United States

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
November 2009

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Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
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I. INTRODUCTION

This guidance is intended to assist manufacturers in responding to the issuance of the United States Pharmacopeia (USP) requirement[2] for the control of residual solvents in drug products marketed in the United States. Specifically, this guidance makes recommendations on the following:

1. How new drug application (NDA) and abbreviated new drug application (ANDA) applicants for noncompendial drug products should limit residual solvents as described in the International Conference on Harmonisation (ICH) guidance for industry *Q3C Impurities: Residual Solvents* (Q3C). This guidance contains recommendations on solvent classification and permitted daily exposure.[3]
2. How manufacturers of compendial drug products that are not marketed under an approved NDA or ANDA can comply with USP General Chapter <467> "Residual Solvents" and the Federal Food, Drug, and Cosmetic Act (the Act).
3. How holders of NDAs or ANDAs for compendial drug products should report changes in chemistry, manufacturing, and controls specifications to FDA to comply with General Chapter <467> and 21 CFR 314.70.

For recommendations on solvent classification and permitted daily exposure, please refer to the ICH Q3C.

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

[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] USP; General Chapter <467> "Residual Solvents."
[3] The levels in ICH Q3C and General Chapter <467> should also be considered for products that are not subject to an NDA or ANDA (e.g., over-the-counter monograph products).

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On July 1, 2008, the USP implemented a requirement for the control of residual solvents in drug products marketed in the United States. The requirement, General Chapter <467> "Residual Solvents," replaced General Chapter <467> "Organic Volatile Impurities." The effective date of this change was July 1, 2008.

III. RECOMMENDATIONS

FDA makes the following recommendations concerning implementation of the USP requirement General Chapter <467> "Residual Solvents."

A. Compendial Drug Products Approved Under an NDA or ANDA

1. *Beginning July 1, 2008, U.S. marketed drug products with an official USP monograph were required to meet the requirements for control of residual solvents as described in General Chapter <467>.*[4]

General Chapter <467> requires control of residual solvents in finished drug products. Although manufacturers may choose to test the drug product, General Chapter <467> also provides options for evaluating the active pharmaceutical ingredient and excipient components of the finished drug product for residual solvents. FDA can accept residual solvent test data on components from tests performed by the drug product manufacturer or the manufacturer may provide test data or, if applicable, appropriate statements obtained from properly qualified suppliers as described in 21 CFR 211.84(d)(2). For example, reports of analysis can be accepted from a properly qualified[5] supplier of a drug product component and will be used by the drug product manufacturer to determine whether the finished drug product complies with the General Chapter <467> defined limits. If the test limits are met for the drug product components, finished product testing is unnecessary.

2. *FDA will accept the use of appropriate analytical procedures other than those included in 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

[4] The Federal Food, Drug, and Cosmetic Act, section 501(b) (21 U.S.C. 351).

[5] As part of ongoing supplier management, a drug product manufacturer is expected to monitor a supplier to assure that the component it produces continues to be of consistent quality and laboratory results reported on the COA remain reliable.

suitability verified under actual conditions of use as described in the current good manufacturing practices (CGMPs) regulations at 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 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.*

Generally, an annual report, if needed, 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. The annual report must contain the information described in 21 CFR 314.70(d)(3). As described in 21 CFR parts 210 and 211, detailed data and information related to control of residual solvents and compliance with General Chapter <467> should be documented and kept available at the manufacturing site for the Agency to review upon request during an inspection.

The annual report should be submitted 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.*

3. *Applicants can submit an amendment to their pending NDA or ANDA to document any changes made to implement 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, General Chapter <467>, and CGMP documentation requirements described in 21 CFR parts 210 and 211. Manufacturers can use appropriate analytical procedures other than those in General Chapter <467> provided they properly describe and validate their procedures and verify their suitability 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

General Chapter <467> does not apply to noncompendial drug products. However, FDA recommends that NDA and ANDA applicants for noncompendial drug products limit residual solvents as described in guidance for industry *Q3C Impurities: Residual Solvents*. Applicants who have not included limits for residual solvents in their NDA or ANDA, as described in 21 CFR 314.50(d), should amend their pending applications as soon as possible.