

Residual Solvents in ANDAs: Questions and Answers (October 28, 2008)

After the revised USP General Chapter <467> Residual Solvents became official as of July 1, 2008, attempts at implementation of this USP chapter have resulted in confusion among ANDA stakeholders. On October 10, 2008, FDA met with IPEC Americas, IPEC Europe, GPhA, CHPA, PhRMA, and SOCMA BPTF¹ to discuss implementation of USP <467>. In addition, FDA received comments from GPhA, PhRMA, APIC², and others requesting additional clarification regarding the implementation of USP <467> for generic drugs. The FDA Office of Generic Drugs (OGD) has carefully considered these comments and suggestions and is providing the following clarifying questions and answers. The clarifications include a flexible, stepwise approach to application of USP <467> to ANDAs to ensure availability of low cost, high quality, safe, and effective generic drugs that meet USP <467> requirements.

Q1: Which ANDAs and ANDA supplements need to comply with USP <467>?

A: ANDAs approved before July 1, 2008 are required to comply with USP <467> if they are the subject of an official USP monograph. ANDAs approved before July 1, 2008 that are not the subject of an official USP monograph should conform to the ICH Q3C Guidance, which has limits for residual solvents identical to those in USP <467>. ANDA sponsors can show compliance with USP <467> in an annual report.

For all ANDAs and applicable ANDA supplements approved between July 1, 2008 and July 1, 2009, ANDA sponsors need to provide information to show compliance with USP <467>. During this time period, however, ANDA sponsors may provide a commitment to verify excipient manufacturer's statements used to support USP <467> compliance within six months of approval. ANDA sponsors will need to submit information supporting verification in a special report³.

For all ANDAs and applicable ANDA supplements approved after July 1, 2009, including tentative approvals, ANDA sponsors will need to have information in the application to show compliance with USP <467> and verification of any excipient manufacturer's statements used to support compliance before approval or tentative approval.

¹ IPEC - International Pharmaceutical Excipients Council
GPhA - Generic Pharmaceutical Association
CHPA - Consumer Healthcare Products Association
PhRMA - Pharmaceutical Research and Manufacturers of America
SOCMA BPTF - Synthetic Organic Chemical Manufacturers Association's Bulk Pharmaceutical Task Force

² APIC - Active Pharmaceutical Ingredients Committee

³ A special report is an update to an annual report, but it is immediately sent to the FDA instead of waiting until the next of submission date for an annual report (see 21 CFR 314.81(b)(3)(ii)).

Q2: What about tentatively approved ANDAs?

A: For ANDAs tentatively approved prior to July 1, 2008, final approval will be granted in accordance with the answer to Question 1. After July 1, 2008 but before July 1, 2009, ANDAs will be granted tentative approval status if they comply with USP <467> and ANDA sponsors provide a commitment to verify excipient manufacturer's statements used to support USP <467> compliance within six months of tentative approval.

Q3: What information should be submitted to demonstrate compliance with USP <467>?

A: For each excipient (for exceptions see Q9) used in the formulation, information in the submission should include:

- Excipient manufacturer's statement regarding residual solvents (See Q4)
- ANDA sponsor's verification of excipient manufacturer's statement (See Q5)

For the drug product, information in the submission should include

- A finished product specification stating compliance with USP <467>
- For each residual solvent identified by the drug substance manufacturer, excipient manufacturer, or used by the ANDA sponsor:
 - A statement that indicates which option was used to demonstrate compliance with USP <467> and a summary of the appropriate calculation, if Option 2 was used, indicating the source of data used in the calculation
 - The results of any residual solvent testing on the drug product, if applicable
- Suitable information to support the safety of residual solvents that are not defined as being Class 1, Class 2, or Class 3 solvents

Q4: What should an excipient manufacturer's statement regarding residual solvents contain?

A: An excipient manufacturer's statement regarding residual solvents should contain:

- All Class 1 solvents used or generated,
- All Class 2 solvents "likely to be present",
- Whether Class 3 solvents are "likely to be present" and the identity of all Class 3 solvents present at greater than 0.5%, and
- All other solvents "likely to be present", as applicable.

Also, in all circumstances:

- The expected control limits for the solvents identified above.

It is preferred that the excipient manufacturer's statement regarding residual solvents is included in the excipient manufacturer's COA, although a separate excipient manufacturer's statement is acceptable. "Likely to be present" refers to the solvents used or produced in the final manufacturing step and to solvents that are used or produced in earlier manufacturing steps and not removed consistently by a validated process.

Examples of acceptable statements include:

- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5 percent.
- Only Class 2 solvents X and Y are likely to be present. All are below the Option 1 limit. (Here the excipient manufacturer would name the Class 2 solvents represented by X and Y.)
- Only Class 2 solvents X and Y and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5 percent.
- No Class 1, Class 2, Class 3, or other solvents are used.

Q5: How can an ANDA sponsor verify excipient manufacturer statements?

A: For each drug product excipient, an ANDA sponsor can choose either of two approaches:

(1) The ANDA sponsor tests the residual solvents as a part of the complete testing protocol in order to demonstrate the capability to perform the tests and to verify the excipient manufacturer's data for each identified residual solvent⁴. Once the excipient manufacturer's data is validated and verified, the ANDA sponsor can implement a valid vendor validation program as per 21 CFR 211.84(d)(2). The ANDA sponsor should submit complete COAs for all excipients, including residual solvent data, in ANDAs and applicable supplemental submissions to demonstrate verification and compliance with USP <467>.

(2) As an alternative, excipient manufacturers or ANDA sponsors can submit evidence that the level of understanding and control of the manufacturing process are sufficient to conclude that the acceptance criteria will always be met provided the process is run within the range of the critical parameters.

An excipient manufacturer's statement that solvents are not used does not require the ANDA sponsor's verification.

Q6: How should the acceptance criterion be established for a residual solvent that is not classified (as Class 1, 2 or 3) in USP <467>?

A: Scientific literature and toxicology data can be used to support the proposed acceptance criterion.

Q7: When is it acceptable to use a Class 1 solvent?

A: Class 1 solvents should be avoided whenever possible. However, an ANDA sponsor or excipient manufacturer may use them if adequately justified. Adequate justification means that the user has diligently evaluated other solvents and provided valid reasons why alternative solvents are not appropriate. Compliance with USP <467> limits is not, in itself, considered adequate justification. The excipient manufacturer should provide a list of Class 1 solvents with specifications and data used in the manufacturing of excipients.

⁴ Note: The reasons for requesting ANDA sponsors to perform the complete testing protocol are twofold, i.e., to verify the actual testing results but, more importantly, to ensure the sponsor has the capability of performing the tests, so that they can run specific tests when problems arise. Without this capability, many firms are inadequately prepared when a problem does arise.

Q8: Can LOD be used to control Class 3 solvents even if Class 2 solvents are present providing that the total of both classes is <0.5%?

A: Yes, provided that the Class 2 solvents are included with the Class 3 total in the loss on drying result and that suitable controls are in place for the Class 2 solvents “likely to be present”. ANDA sponsors should be aware that unidentified Class 3 solvents may interfere with analytical methods to measure Class 2 solvents.

Q9: How should residual solvents in coating materials, colorants, flavors, capsules, and imprinting inks be characterized?

A: Information of residual solvents in coating materials, colorants, flavors, capsules, and imprinting inks is generally not needed unless Class 1 solvents are used in the manufacture of these components.

Q10: Should residual solvent test methods used by ANDA sponsors be validated or verified?

A: Non-USP methods should be validated. USP methods should be verified (see USP <1226>).

Q11: Would it be acceptable to use a high purity solvent in place of the USP reference standard?

A: Yes, a high purity solvent may be used in lieu of the reference standard if suitable documentation (i.e., certificate of analysis) of the purity and source is provided.

Q12: If a drug product utilizes excipients supplied in solvents and the solvent is then driven off during the drug product manufacturing steps, does the final drug product need to be tested and do all the limits in USP <467> apply?

A: For excipients supplied in solutions, the solvent is considered a component in the drug product manufacturing process and therefore USP <467> applies to this solvent. The removal of the solvent by the drug product manufacturing process should be demonstrated by either drug product testing or an ICH Q8(R) QbD-based approach.