USP Chapter <467> Residual Solvents - Additional Information

After the revised USP Chapter <467> *Residual Solvents* became official July 1, 2008, attempts at implementation of <467> have resulted in variability in the information being submitted to applications, and to uncertainty regarding what information would be considered satisfactory for demonstrating compliance with that chapter. The Office of Generic Drugs has decided, in order to minimize the need for additional submissions and review caused by this situation, to provide the following additional information. This information is intended to facilitate preparation and review of adequate submissions by clarifying OGD expectations regarding implementation of USP <467>.. Please note that control of residual solvents is also required for drug products and ingredients which are not described by a USP monograph.

General considerations:

1. Unapproved (both new applications and pending) original applications (and amendments) that do not demonstrate compliance with USP <467> are considered deficient.

2. All supplements and supplement amendments submitted beginning July 1, 2008 for which an acceptable drug product specification or drug product certificate of analysis would be necessary for approval, but which do not demonstrate compliance with USP <467> will be considered deficient

3. Dependence by the applicant on vendor statements and/or vendor COAs that USP <467> is met, without verification by the applicant, does not demonstrate compliance and will be considered a deficiency.

   EXCEPTION: Vendor statements to the effect that certain solvents are not used do not require applicant verification. Additionally, statements regarding compliance with USP <467> are assumed to also address solvents that are not designated as being Class 1, 2, or 3.

4. In general, a commitment by the applicant to meet USP <467>, either for original applications or relevant supplements, does not demonstrate compliance and will be considered a deficiency.

   EXCEPTIONS:

   Applications otherwise acceptable for Tentative Approval may be granted Tentative Approval status if there is a commitment to demonstrate compliance prior to final approval. (Final approval is not granted until commitment is fulfilled).

   In the case of PEPFAR products, a Tentative Approval may be granted if there is a commitment made to demonstrate compliance within 6 months of the tentative approval date. This extension reflects the critical role of these products in treatment of a significant medical emergency

Submission Content

A submission would be considered complete for the purpose of demonstrating compliance with USP<467> if it contains the following information. Information, if available, from vendor validation programs verifying the integrity of vendor supplied information may be used where appropriate..

For each ingredient used in the formulation:

- Manufacturer's COA listing all solvents used in manufacture of the ingredient/s or a statement that no solvents are used in the manufacture.

- Applicant's updated COA for the ingredient/s including solvent identity, acceptance criteria and analytical method~~).~~ Loss on drying would be acceptable if only Class 3 solvent/s is used in the manufacture of an ingredient. Class 3 solvents are also to be named.

- Applicant's test data for solvents, including data for class 3 solvents, should be submitted for all ingredients.

- Applicant's method verification data for USP method and method validation data if non-USP methods are used

- Demonstration that the ingredient/s meets <467> option 1 or option 2.

- An updated finished product specification stating compliance (including option used) with USP<467>.

- Suitable qualification information to support residual solvents which are not defined as being Class 1, Class 2, or Class 3 solvents, that and are present at exposure levels greater than 1.5 micrograms per day.

- For nonfunctional coating materials, colorants, and flavors, testing of residual solvents present in any ingredient of the component is not necessary.