DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

To All Interested Parties:

As you are aware, there has been a proposed Chapter from the U.S. Pharmacopeia (USP) for control of residual solvents in drug products (See Attached Text). The effective date for this requirement has been postponed a number of times. However, beginning July 1, 2008, it will go into effect and all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual USP monograph.

This Chapter, <467>, addresses levels of residual solvents acceptable for drug products official in the USP (i.e., drug products for which there is a USP monograph) to assure the safety of the drug products. The Chapter is derived from the International Conference on Harmonization (ICH) Q3C quality guidance.

With the Chapter becoming effective, it will be necessary for the Office of Generic Drugs to assure this safety information is addressed in abbreviated new drug applications (ANDAs). Therefore, starting July 1, 2008:

- any new ANDA must provide information and data as necessary to demonstrate control of residual solvents prior to approval (or tentative approval).
- ANDAs currently under review, but are not yet approved by July 1, 2008, must also contain this information and data as necessary.
- residual solvent information and data as necessary for approved products should be submitted in the next annual report for the ANDA.

The specifications for residual solvents in ANDAs should:

- Ensure that all drug substance and excipient components of the drug product, have residual solvent acceptance limits that fall within the ICH Q3C (option 1) limit[1], or
- Ensure that all drug substance and excipient components of the drug product, weighted by their amount in the drug product, results in a cumulative daily exposure for residual solvents that falls within the ICH Q3C (option 2) limit, or

[1] This approach requires that the total daily dose of the drug product be less than 10 g/day

- Ensure via direct testing of the drug product, that the total daily exposure for residual solvents falls within the ICH Q3C (option 2) limit.[2]

In addition, sponsors should include a commitment to re-assess their compliance with USP <467> if they change ingredient suppliers in the post approval period including implementing revised controls, if appropriate**.**

While the USP Chapter <467> specifically addresses drug products that are covered by a monograph in the USP, to assure safety of all products and for consistency of review, OGD also expects ANDAs for products not official in the USP to contain information and data as necessary that assures safe levels of residual solvents in the drug product consistent with USP <467>. The same timelines and expectations for submission will apply to noncompendial products.

Your cooperation is appreciated.

Gary Buehler
Director
Office of Generic Drugs

[2] Direct testing for residual solvents in the drug product (or via applicable in-process tests) should be employed for those solvents used in the manufacturing process of the drug product.

Text of Notice

The following statement is contained in General Notices and Requirements (Tests and Assays section) of the USP:

> "Residual Solvents–The requirements are stated in Residual Solvents <467> together with information in Impurities in Official Articles <1086>. Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in Residual Solvents <467>, using the general methods presented thereiother suitable methods."