

Regulatory Basis:

FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion

This document provides guidance in offloading, use and recovery of solvents used in the commercial manufacture of Active Pharmaceutical Ingredients (API) and intermediates. The processing and use of solvents should be established, controlled and monitored based on the potential impact on intermediate or final API product quality.

1. Prerequisites for Solvent Recovery Process Validation include, and are not limited to, the following:
 - Approved production Instruction-Records and applicable SOPs;
 - Identification of all solvent recovery Critical Process Parameters;
 - Qualification of direct impact equipment, facilities and systems, (including computerized systems). Verification of completion of equipment qualification should be included in the validation protocol; exceptions to this requirement should be approved by the Validation Committee (VC);
 - Approved specifications for finished recovered solvent product and in-process testing;
 - Validated test methods used to demonstrate quality requirements; and
 - Personnel taking part in the validation work should be trained and qualified before carrying out such work, with training records documented.

2. Validation Protocol Contents should include or reference, but not be limited to the following:
 - Definition of the solvent:
 - Specifications;
 - In-process control specification;
 - Critical solvent recovery process steps;
 - Critical process parameters and Operating Ranges, including justification for these parameters and ranges or reference to other documents that include the justification;
 - Intended use(s) of the recovered solvent; and
 - Spent solvent stream selection criteria.

3. When Required, Volatile and Non-Volatile Impurity Limits for Recovered Solvent (see Table 1), should be supported by documented scientific rationales and/or data and approved by the Quality Team. Dose, toxicity and weight percent of the potential impurities should be considered when setting limits for volatile and non volatile impurities.

4. Validated Solvent Recovery Processes that undergo major changes to incoming used solvent streams (e.g., those requiring a new solvent recovery process, or a stream that does not fit established criteria) require revalidation. In addition, major changes to equipment, facility, procedures or the solvent recovery process may require revalidation. Minor changes may not require revalidation but may require a documented, expanded test program or other formal evaluation.

5. Solvent Stored in Bulk Storage Tanks, that are being actively used, should be re evaluated at least once per year. Inactive solvents (e.g., solvents that have not been used within a period of 3 months) should be re evaluated prior to use.