Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion:

This document provides an example of the documentation for validation of a solvent recovery process. Solvent recovery validation is needed in some situations such as where the recovered solvent is intended for general site wide reuse into suitable manufacturing processes, including other API manufacturing processes than those from which the used solvent originated.

This document provides an example of the contents that may be found in solvent recovery validation documentation, including appropriate acceptance criteria for solvent recovery validation. The processing addressed by this type of validation includes the recovery of used solvent to provide solvent that is acceptable for use.

This document applies only to solvent recovery validation and is not intended to describe validation practices for API or drug product manufacturing.

Information on solvent recovery for API manufacturing may be found in another document that describes solvent recovery practices and includes considerations for setting impurity limits for recovered solvent. Internal impurity limits for used solvent intended for recovery are established based on knowledge of the capability of the intended recovery process and the intended use of the recovered solvent.

In general, to begin the work process for validation of a solvent recovery process, a documented description of the recovery process should be provided. This should include explanation of the controls that ensure that the recovery process can reliably provide acceptable quality recovered solvent that is suitable for its intended uses. Justification should be provided for processing parameters that are critical for control of recovered solvent quality. A validation protocol with acceptance criteria for demonstrating consistent control of the recovery process then provides the plan for evaluating validation batches, much like protocols for validation of manufacturing processes.

Process consistency:
If the potential for significant variability in the feedstock of used solvent exists, it is recommended that validation batches be prepared over a significant period of time to encompass the likeliness for variability in the used solvent feedstock. A good practice that has been used is to include validation batches made with an intervening time interval between each, as shown in the example provided later in this document (see acceptance criteria section). The increased risk introduced by potential variability in feedstock is therefore addressed by evaluating more validation batches over a longer time period.

Concurrent validation;
Concurrent validation is typically appropriate for solvent recovery validation. Validation may typically be done over an extended period of time rather than necessarily including consecutive batches, and releasing individual solvent batches that meet validation acceptance criteria pose no appreciable risk to customers of our API and drug products (i.e. solvent is a raw material rather than a final product).

Process controls:

provided or referenced in the solvent recovery validation protocol. As an example, specifications for the THF/toluene feed for the THF recovery process are summarized in the table included in **Appendix II.**

Critical Process Controls:

In preparation for the final distillation, information on the composition of each batch of used solvent to be distilled is needed. For THF recovery, the computer simulation does not account for isopropyl alcohol (IPA) in the stream, so it is critical that the amount of IPA is NMT 0.1 vol-%. Feed composition that is higher in IPA will negatively impact the quality of recovered THF by being unacceptably high in the total alcohols (C1-C4) specification. Used THF/toluene streams with higher amounts of IPA should be directed through the optional processing step for removal of alcohols (see Scheme I in **Appendix I).**

Slop cuts are described earlier in the process overview and are important to the success of the process but some tolerance for variation in where these cuts are started and ended will not be harmful to the quality of the recovered THF. However, the product cut start can negatively impact quality if begun too early by permitting capture of off-specification material. A late product start cut will not affect quality, only resulting in loss of yield. When the product cut is started is therefore a critical process control.

A Data Control System (DCS) or appropriate testing of samples may be used to control the various reflux ratios based on the recipe parameter setting by modulating the control valve as needed to achieve the specified reflux ratio. With or without DCS, it is important not to run with too low a reflux ratio (less than 2:1) for an extended period (i.e. running the distillation too fast), which could risk adding low-specification material to the product cut. Short-term deviations will only have a minor impact on quality. There is no adverse quality impact from running the reflux ratio higher than the prescribed 3:1. A high reflux ratio results in a slower distillation and slow product recovery, but this has no detrimental quality impact on the recovered solvent.

The end of the second product cut should occur when a column temperature of 75 ºC is reached. Ending the product cut earlier will result in loss of yield, but no detrimental quality impact. If the temperature exceeds 76 ºC and the product cut has not been completed, quality of the THF product cut could be diminished. This temperature is regarded as a critical process control.

To summarize, two critical process controls have been identified for the THF-COL5 recovery process:

Process Control and Acceptable Range	**Why Chosen**
Start of first product cut: Slop cut volumes NLT simulation values or GC of distillate NLT 99.3 vol-% THF, NMT 0.25 vol-% ethanol, and NMT 0.03 vol-% water	If started too early, low specification material can be added to the product.
End of second product cut: Middle column temperature NMT 76 ºC	If allowed to continue further, low-specification material can be added to the product

Validation Plan and Acceptance Criteria

To validate this solvent recovery process, THF will be recovered from three sets of at least three consecutive batches of used THF. The time period between the beginning of

Appendix II. Volatile impurity specifications for Used THF to be Recovered

Component	Specification	Comment
Methylene chloride	NMT 1.0 vol-%	With higher amounts of methylene chloride, recovered THF may not meet its methylene chloride specification of NMT 0.2 %.
t-Butanol	NMT 0.1 vol-%	Separation of t-butanol from THF is poor in this process.
Cyclohexane + 2,3-dimethylpentane	NMT 0.75 vol-%	Separation of these components from THF is poor in this process.
Methanol	NMT 0.02 vol-%	Methanol is separated from THF with a preliminary distillation. A series of total refluxes and slop cuts are performed until the methanol content meets the NMT 0.02% limit. This is necessary to prevent formation of methyl propionate in the THF for DMAP processing step (used to diminish amounts of other alcohols). Methyl propionate cannot be distinguished from THF by the GC assay method used, which could result in a false GC assay result for THF.
C1-C4 alcohols	NMT 0.05 %	This includes methanol, ethanol, isopropanol, and butanols. If the THF feed is higher in alcohols before beginning the product cut, the THF product may not meet the total alcohols specification. Ethanol and isopropanol are controlled using the THF for DMAP processing step, by DMAP-catalyzed reaction with propionic anhydride to form higher-boiling propionate esters.
Water	NMT 0.5 vol-%	Water is not easily removed from THF in this process. Quality of the THF product is not diminished if the THF feed contains 0.2 to 0.5% water, but yields are reduced. THF feed higher in water is sent through a caustic drying step prior to being acceptable for distillation.

