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:
A computer simulation is sometimes used to predict volumes where fractional cuts in the distillate should be made. The simulation typically uses analytical data from analysis of the used solvent feed batch and known analytical requirements established for the start of each cut. When a simulation is used, it is recommended that the effectiveness of the computer simulation to predict process control points be shown.

Alternatively, in-process gas chromatograph (GC) solvent, Karl Fisher (KF) water, or other analytical methods for evaluation of distillate samples may be used to determine cut points, if a computer simulation is unavailable. Either in-line or off-line testing may be used. It may be helpful to perform a lab-scale feasibility run to predict where to make distillate cuts. Where a continuous recovery process is used, other operating parameters than cut points (e.g., feed rates, reflux rate, and/or column temperature profile) may be important process controls that should be defined to insure control of the quality of recovered solvent.

Validation of any process is dependent on the particular systems used for the process, and validation of solvent recovery operations is not different in this regard. Controls and decision criteria may need modification if the distillation is run with a different column, for instance. When validation of the solvent recovery process is needed, an impact assessment of the systems used for a solvent recovery process should be performed to determine if they could directly impact the quality of an API.

Acceptability:
Validation batches should conform to release specifications established for the recovered solvent. These specifications should include tests for volatile and non-volatile impurities. A concluding validation report should evaluate how each of the acceptance criteria was met.

Validation of the use of recovered solvent should be done as part of validating the process in which it is used, if this is considered necessary.

Example: THF recovery process
The remainder of this guidaqnce provides one example of validation of a batch solvent recovery process that of the recovery of tetrahydrofuran (THF) from a used THF/toluene mixed solvent . The used THF may be derived from multiple process streams and the recovered THF will be available for mult-process use. While this example includes the use of computer simulation to predict when to make cuts for collection of distillate fractions, validation of the process may also be achieved with appropriate in-process monitoring.

Control limits for impurities permitted in the used THF stream and for the in-process stream acceptable for final distillation are established at different points in the solvent recovery process based on where impurity controls are established. See **Appendix I** for a diagram of this THF recovery process and **Appendix II** for impurity control limits for used THF to be recovered.

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 the last batch in a set and the first batch of the next set will be at least one month. The total number of batches will therefore be no less than nine.

Acceptance criteria:

- No significant deviations from the master instructions for the THF recovery process are acceptable.
- Critical process parameters must be controlled within the ranges specified in the table above.
- The suitability of each feed batch for this recovery process will be examined. For each batch used for the validation, the computer simulation (or in-process control, where computer simulation is not used) must predict that acceptable THF can be produced.
- Acceptability of the recovered THF will be shown by evaluating the results of the release testing on the representative sample for each batch. Each batch must meet these release specifications for THF:

GC Tetrahydrofuran	NLT 99.0 area-%
Moisture (by KF)	NMT 0.03 vol-%
Non-volatile components	NMT 0.0035 %
APHA (color)	NMT 20
Peroxides	NMT 150 ppm
Impurities (by GC):	
Methylene chloride	NMT 0.2 area-%
Alcohols (C1-C4)	NMT 0.15 area-%
Acetone	NMT 0.05 area-%
Total ketones	NMT 0.1 area-%
Other volatile impurities:	
Individual unidentified	NMT 0.2 area-%
Total unidentified	NMT 0.2 area-%

- Consistency of the recovery process will be shown by the successful completion of no less than three consecutive batches in each of the sets of recovery runs (or not less than nine batches total). All validation batches must meet the requirement described above.

