Summary - Equivalence Criteria of Impurities for API Process Validation

This guidance provides recommendations for demonstrating equivalence of impurities to historic batches during validation of API processes for small molecules.

Existing impurities meet registered specifications when:

- There are fewer than ten historical reference batches, or;
- Reference data may not be representative of current process capability, or;
- The quantitative reference data do not exhibit a symmetrical distribution.

A more detailed discussion of these guidelines follows, along with recommendations to assist with statistical evaluations. batches and analytical tests for the equivalence comparison. For validation of a process to prepare a new API, the impurity profile should be comparable For some validations, insufficient reference batches are available for a meaningful comparison. For other validations, the availability of adequate reference batch data makes the use of statistical acceptance criteria more desirable because it enables comparison of the validation batches to established process capability data.

For validation of a process to prepare a new API, the impurity profile should be comparable to or better than the profile determined during process development, or for batches used for clinical or toxicological studies. For evaluation of a newly developed or modified process to prepare an API that is already commercially distributed, the comparison provides assurance that the process produces material that is equivalent to (or better than) acceptable material prepared in the past by an existing process, with respect to impurities.

Rejected, reprocessed, and reworked batches generally should be excluded from the historical set because they are generally not representative of the results expected from normal processing. Removing such batches for cause is permissible (thus breaking the consecutive nature of the batches), but batches should never be arbitrarily added to or excluded for the purpose of influencing the historical ranges of analytical results.

For residual solvents, a statistical acceptance criterion may not be appropriate in the validation of process changes that impact product drying. An acceptance criterion of “meets specifications” may be preferable in this situation. A process change that involves introduction of one or more new solvents to the process requires different considerations, and will usually require that registration specifications and/or ICH (Q3C) guidelines be met for the new residual solvent(s).

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