and maximum values) when:
- There are ten or more reference batches with a non-Gaussian distribution of quantitative data, but there is confidence that the data are representative of current process capability.
3. Existing impurities meet specifications and are within the statistical limit (mean +/- three standard deviations) when compared to reference data when:
- There are ten or more reference batches with a normal (Gaussian) distribution of data, and there is confidence that the data are representative of current process capability.

A more detailed discussion of these guidelines follows, along with recommendations to assist with statistical evaluations. Other specific recommendations include selection of reference batches and analytical tests for the equivalence comparison. A more detailed summary of recommendations is provided in **Appendix I,** and a statistical evaluation of sample data to illustrate one approach for performing the equivalence comparison is provided in **Appendix II.**

Recommendations and Rationales

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.

The need to evaluate equivalence for isolated process intermediates should be considered on a case-by-case basis.

For some validations, insufficient reference batches are available for a meaningful comparison. Meeting established limits is considered adequate for the equivalence comparison in these situations. 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.

A.   Selection of appropriate reference batches:

1.   **New Products** (new API or intermediate process at first manufacturing site)
Batches prepared during process development should be selected. These may include batches prepared in Production equipment, and those prepared at laboratory and pilot scale. They should be batches made by the same process and may include pivotal clinical batches, and those used for toxicological and/or stability studies. In many cases, the number of acceptable development batches may be relatively small.

2.   **Existing APIs**
a)   Major changes undergoing revalidation, or first-time validation – Reference batches should be selected from plant batches prepared prior to the validation to be performed.

Appendix II. Example of statistical analysis of impurity and purity data for equivalence evaluation

This table shows historical HPLC purity and impurities and residual solvents data. Note that lot 1008 was rejected and therefore omitted from the table. See also explanatory notes below and on next page.

ID →	API Impurity Profile (HPLC method xxx)						Residual solvents (GC method yyy)	
	Impurity A	Impurity B	Impurity C		Impurity D	Total Imps	THF	Methylene chloride
RRT →	0.35	0.67	1.31	1.76	2.67			
Release limit	NMT 0.5%	NMT 0.3%	NMT 0.2%	NMT 0.1%	NMT 0.3%	NMT 1.0%	NMT 0.5%	NMT 600 ppm
Historical batches								
1001	0.06	0.08	BQL	0.13	0.15	0.59	0.20	310
1002	0.07	0.07	BQL	0.05	0.22	0.54	0.22	244
1003	0.08	0.07	BQL	0.12	0.15	0.62	0.18	LT 200
1004	0.10	0.11	BQL	0.10	0.08	0.63	0.17	379
1005	0.15	0.27	BQL	BQL	0.12	0.84	0.18	217
1006	0.40	0.12	BQL	0.07	0.08	0.75	0.19	LT 200
1007	0.15	0.10	BQL	BQL	0.07	0.42	0.16	LT 200
1009	0.22	0.18	BQL	BQL	0.07	0.61	0.19	286
1010	0.15	0.08	BQL	BQL	0.08	0.42	0.21	211
1011	0.08	0.12	BQL	BQL	0.05	0.59	0.20	LT 35
Mean	0.146	0.120	BQL	0.047	0.107	0.601	0.190	164.7
SD	0.102	0.062	--	0.054	0.053	0.129	0.018	149.6
Mean+3SD	0.45	0.31	--	0.21	0.26	0.99	0.24	613.5
Mean-3SD	--	--	--	--	--	--	--	--
Equivalence acceptance criterion	NMT 0.4% **	NMT 0.3% **	NMT 0.2% ***	NMT 0.1% #	NMT 0.3% ***	NMT 1.0% *	NMT 0.3% ##	NMT 600 #

NMT = not more than; LT = less than; NLT = not less than; BQL = beneath quantitation limit (or none detected); RRT = relative retention time.

* = Acceptance criterion is the mean +/- 3 SD value determined from above historical data.

** = Acceptance criterion is historical maximum (or minimum) value. For Impurities A and B, one historic result is significantly different than the others, distorting the mean + 3 SD calculations, so the maximum values are suggested as equivalence criteria. (Max., mean + 3 SD, and release limit are the same for Impurity B.)