Essentials in Tolerance Design and Setting Specification Limits

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Setting Specification Limits Rationale and Application Areas

The purpose of this article is to provide an overview of methods for setting specification limits and acceptance criteria for drug release testing, systems suitability/validity for analytical methods, process limits for in process control and monitoring and process limits for cell culture, purification and other unit operations including raw materials and reagents. It is recommended that limits are set early in drug development (Phase I) and refined in latter phases (Phase II and III) as data becomes more available. In defining what a specification is ICH Q6B (1) states:

> "A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval."

In addition, Q6B points out the following application areas for specification limits:

1. *Specifications are linked to preclinical and clinical studies.*

2. *Specifications are linked to analytical procedures.*

3. *Specifications are linked to a manufacturing process.*

4. *Specifications should account for the stability of drug substance and drug product.*

ICH Q8 (2) says the following regarding Critical Quality Attributes, distributions and limits:

> *"A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."*

Systematic Drug Development

Thinking about systematic drug development if can be routinely characterized by three basic activities, 1) system design, the method by which the product is synthesized, formulated, processed and measured, 2) parameter design, the critical attributes or parameters and targets that achieve all CQAs, 3) tolerance design, the acceptable range for each critical attribute or parameter that will assure all CQAs will be within limits without out of specification (OOS) events. Tolerance design is the focus of this paper and discussion. A tolerance is the distance from the upper specification limit to the lower specification limit. When a tolerance is defined there is a clear target. For a one-sided specification the goal is to maximize or minimize performance (i.e. purity or impurity) there is no clear target and therefore margin is measured rather than tolerance. Margin is defined as the distance from the mean performance to the nearest specification limit.
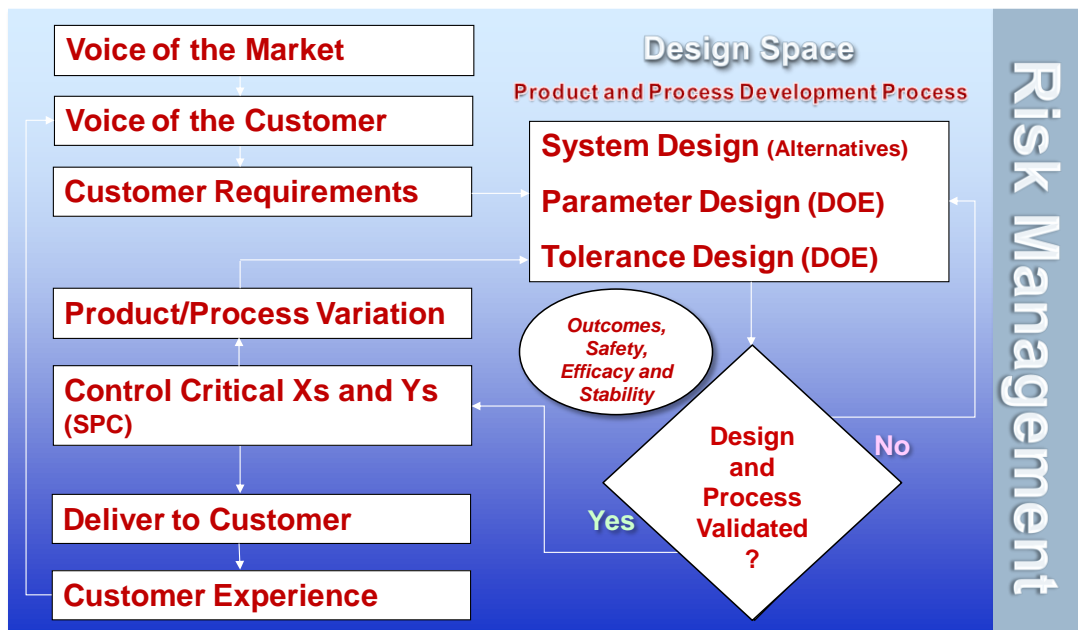

Figure 1.0 Systematic Drug Development

Methods of Setting Tolerances and Limits

There are six methods typically used for setting limits and the they are listed in order of preference, the first method being most desirable and the last method is least desirable.

1. *Set specification limits based on transfer functions and associated margin analysis. Limits have a clear link to clinical PK studies or linked from CQAs to unit operations.*
2. *Set specification limits based on statistical distributions and analysis.*
3. *Set tolerances based on a worst case margin analysis.*
4. *Set tolerances based on a percentage of the mean (±10% or ±20%).*
5. *Guess at tolerances and set arbitrary limits.*
6. *No tolerances and* no targets, *quality levels are vague or undefined.*

Ideally all limits should be based on a transfer function, correlation or model. It expresses the relationship of how variation in the factor (X) transmits variation onto the response (Y). Limits are used as part of the control plan to control the variation in the product, process or assay. Statistical distributions are also a valid approach to limit setting; however, it requires that there are no adverse outcomes linked to the parameter of interest. It is reasoned that if the variation of the product, process, method or raw materials does not result in poor or adverse outcomes, then the variation present in the samples data must be acceptable. When adverse outcomes are linked to a parameter, statistical distributions should not be used to set limits. Tolerance design should begin with all CQAs for release testing of drug substance and drug product and then flow down to all unit operations, assays/analytical methods, formulation, raw materials and equipment settings. Where possible CQAs and drug attributes should be linked to PK clinical studies, a sound scientific rationale and or prior knowledge.

Guidance on Setting Limits

ICH Q6B 2.6 further states:

> *"Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented."*

Statistical tools such as SAS or SAS/JMP are recommended when setting limits. Excel or other spreadsheet tools lack a robust set of tools for setting limits and incorrectly assume normal distributions when they are often nonnormal.

Risk and Setting Limits

There is a direct relationship between limit setting and risk. ICH Q9 (3) Quality Risk Management suggests using risk as a consideration in product development. The wider the interval the greater the amount of transmitted variation on the Y response, thus wider intervals should only be used when the risk of OOS or clinical risk is medium to low. The following table provides the statistical basis for the interval in K sigma and likelihood of failure and resulting OOS levels. In general K sigma design margin of 1 or even 1.5 is very desirable where possible. OOS PPM should be targeted at 100 or less for every CQA.

Limits	z Score	OOS PPM	Failure Rate %	Quantiles (probability)	Cpk	Sigma Quality	K Sigma	Tolerance Interval Confidence/ Population	Risk	K Sigma Design Margin
Upper	2	22,750	2.2750132%	0.9772498681	0.67	3.5	2	95/93	Very High	-1
Lower	-2	22,750	2.2750132%	0.0227501319	0.67	3.5	2	95/93	Very High	-1
Upper	3	1,350	0.1349898%	0.9986501020	1.00	4.5	3	95/99	High	0
Lower	-3	1,350	0.1349898%	0.0013498980	1.00	4.5	3	95/99	High	0
Upper	4	31.7	0.0031671%	0.9999683288	1.33	5.5	4	95/999	Medium	1
Lower	-4	31.7	0.0031671%	0.0000316712	1.33	5.5	4	95/999	Medium	1
Upper	4.5	3.40	0.0003398%	0.9999966023	1.50	6	4.5	95/99974	Medium	1.5
Lower	-4.5	3.40	0.0003398%	0.0000033977	1.50	6	4.5	95/99974	Medium	1.5
Upper	5	0.29	0.0000287%	0.9999997133	1.67	6.5	5	95/99995	Low	2
Lower	-5	0.29	0.0000287%	0.0000002867	1.67	6.5	5	95/99995	Low	2
Upper	5.5	0.02	0.0000019%	0.9999999810	1.83	7	5.5	95/99999	Low	2.5
Lower	-5.5	0.02	0.0000019%	0.0000000190	1.83	7	5.5	95/99999	Low	2.5
Upper	6	0.00	0.0000001%	0.9999999990	2.00	7.5	6	95/9999985	Very Low	3
Lower	-6	0.00	0.0000001%	0.0000000010	2.00	7.5	6	95/9999985	Very Low	3

Table 1.0 Probability and Risk Table for Setting Limits

Tolerance Interval Approach

Tolerance intervals were developed to provide a correction for limited sample sizes and scales the interval of risk based on three considerations: 1) sample size, 2) confidence interval and 3) proportion of the population to be described.

NIST (4) defines a tolerance interval as:

> "There is also a way to cover a fixed proportion of the population with a stated confidence. Such an interval is called a tolerance interval. The endpoints of a tolerance interval are called tolerance limits. An application of tolerance intervals to manufacturing involves comparing specification limits prescribed by the client with tolerance limits that cover a specified proportion of the population."

Tolerance intervals should be used under the following conditions:
1. No transfer function is available and/or possible.
2. No adverse nor unacceptable results are associated with the parameter or response.
3. Sample size is less than 30, tolerance intervals should not be used when $n \geq$ than 30 as they will be too tight and fail to correct for n. Use K sigma when $n \geq 30$.
4. Sample data is stable (use a control chart or regression analysis to evaluate stability)
5. Distribution is either normal or nonnormal

Tolerance interval procedure:
1. Make sure you have a representative sample of the population of interest
2. Confirm there are no compendial limits nor requirements specified by guidance. If so use the compendial limits.
3. Outlier removal precedes distribution fitting and evaluation, Grubbs or Dixon's Q test.
4. Determine the distribution that best fits the data, normal or nonnormal distribution, use a goodness of fit or AICc functions to determine the best fit.
5. Avoid using Johnson or lognormal distributions when fitting nonnormal tolerance intervals as they are set limits excessively wide. Normal, Gamma, Weibull, Normal Mixture are preferred and should all work well to set limits.
6. Using the table above determine the risk and associated tolerance interval and margin
7. Use a K Factor calculator (5) to determine K for the interval (n, confidence and population)

8. Set Spec using K Sigma to define the limits
9. Compare results to compendial or historical limits for the drug attribute or process parameter

% HMW Tolerance Interval Example n=12

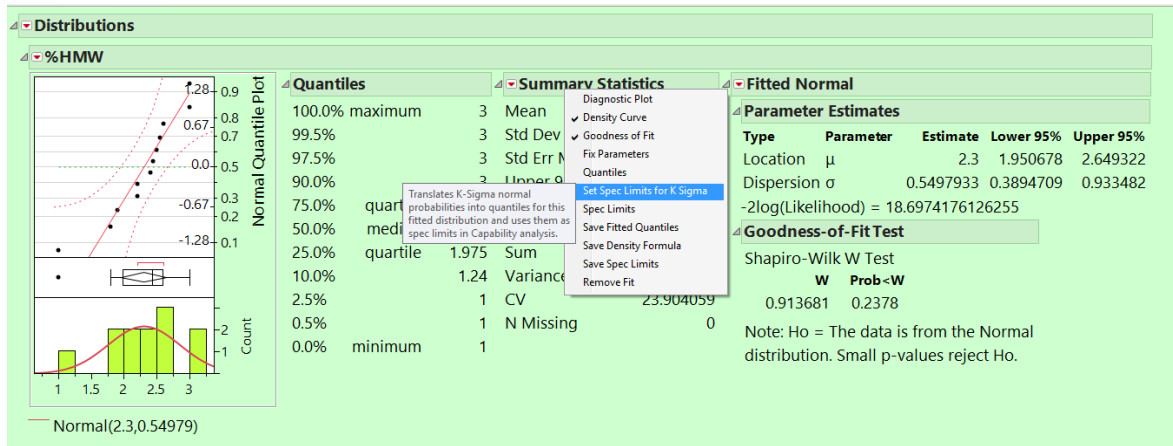| No of Sides	Sample Size	Confidence Interval	Proportion of the Population	K Factor
Two	12	0.95	0.999	5.311
One Upper	12	0.95	0.999	4.900
One Upper	12	0.95	0.999	4.900

Table 2.0 K Factor Calculation

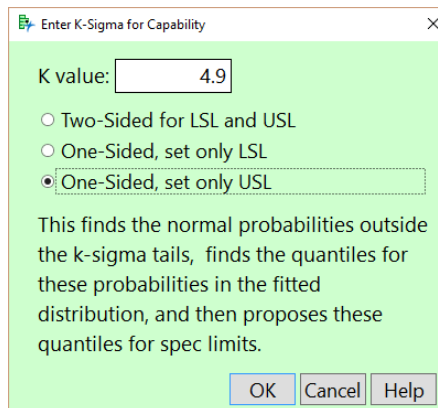Figure 2.0 Fitting the Normal Cuve and Setting the Tolerance Interval

Figure 3.0 Setting the K value and Type of Limit

%HMW

Fitted Normal

Goodness-of-Fit Test

Shapiro-Wilk W Test

W	Prob<W
0.913681	0.2378

Note: Ho = The data is from the Normal distribution. Small p-values reject Ho.

One Sided 95/999 Tolerance Interval

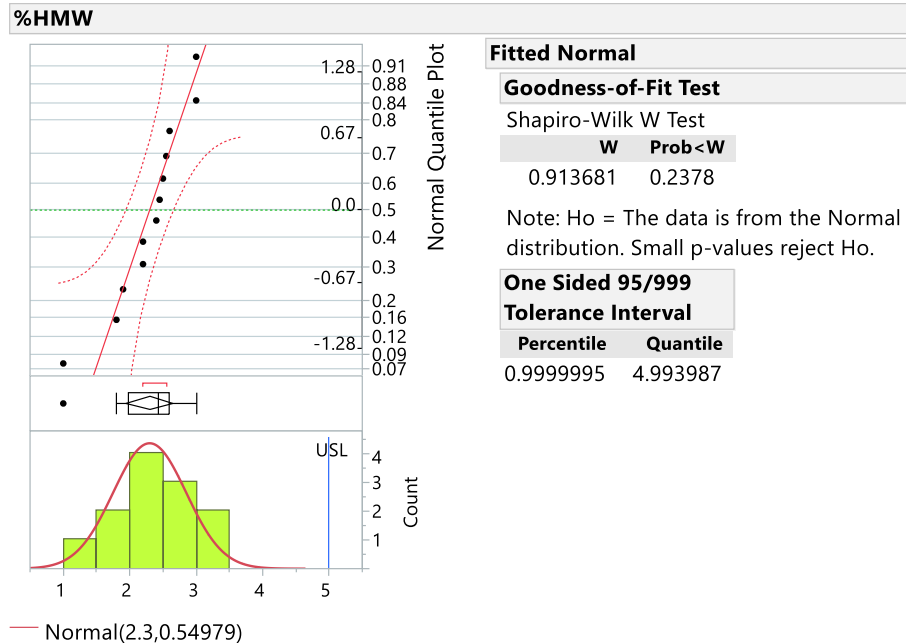| Percentile	Quantile
0.9999995	4.993987

— Normal(2.3,0.54979)

Figure 4.0 One Sided 95/999 Tolerance Interval for %HMW

K Sigma Approach

K sigma approach is similar in every way to a tolerance interval except it uses the K sigma value from Table 1.0 and does not correct for sample size, confidence interval nor proportion of the population. There is no need for sample size correction once the sample size is above 29.

Setting Limits using a DOE or Regression Transfer Function

A transfer function is the best way of predicting the influence of how changes in X influence the change in the response. Transfer functions may be generated based on a designed experiment and fitting a model to the data or by other regression techniques.
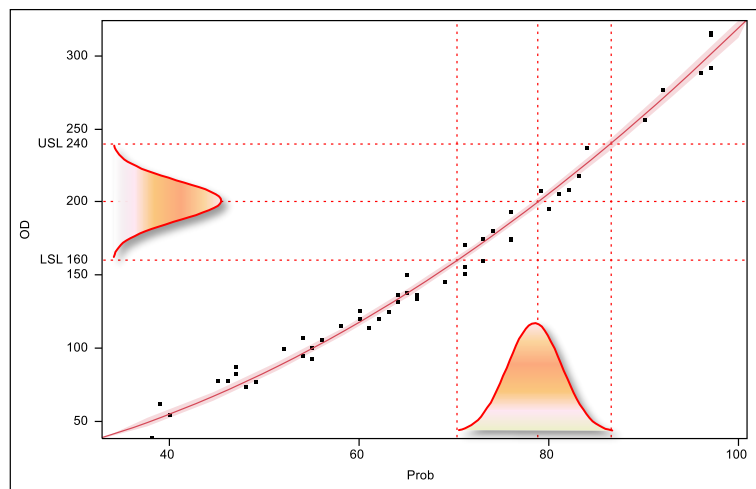

Figure 5.0 Transfer Function

The following is the procedure setting limits using a transfer function and a statistical package such as SAS/JMP.

1. Using a structured designed experiment generate the transfer function or model equation.
2. Load the model into a profiler and use the profiler to set limits
3. Optimize the settings to achieve excellent results in the response and set the target
4. Turn on the simulator function to set limits
5. Determine one sigma variation for each factor at the optimal set point. If not using a normal sources of error, add the parameters of the curve being used
6. Add the root mean squared error to the analysis
7. Defined the likely distribution of the X parameter, if processing to target use a normal truncated distribution if processing to range use a uniform distribution
8. Restrict the range of X at the set point until all responses indicate a PPM of <100 per parameter. This is done for all critical process parameters, method parameters etc.
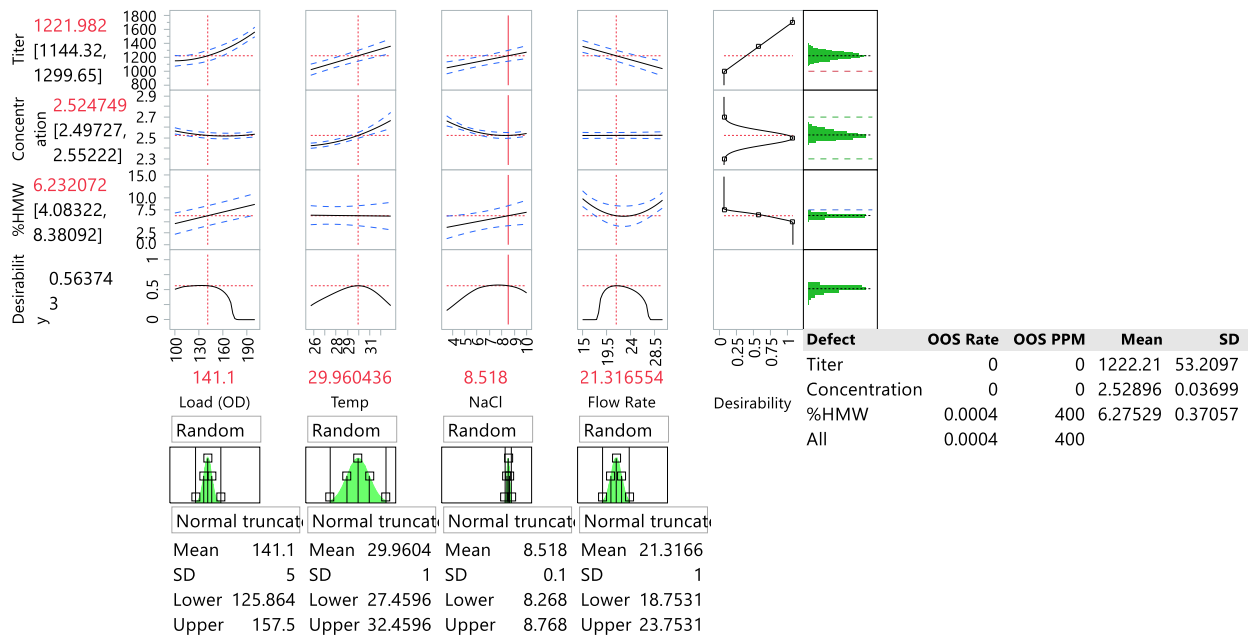
Defect	OOS Rate	OOS PPM	Mean	SD
Titer	0	0	1222.21	53.2097
Concentration	0	0	2.52896	0.03699
%HMW	0.0004	400	6.27529	0.37057
All	0.0004	400		

Titer 1221.982 [1144.32, 1299.65]
Concentration 2.524749 [2.49727, 2.55222]
%HMW 6.232072 [4.08322, 8.38092]
Desirability 0.563743

Load (OD)	Temp	NaCl	Flow Rate	Desirability
141.1	29.960436	8.518	21.316554	

Random | Random | Random | Random

Normal truncated | Normal truncated | Normal truncated | Normal truncated

Mean	141.1	Mean	29.9604	Mean	8.518	Mean	21.3166
SD	5	SD	1	SD	0.1	SD	1
Lower	125.864	Lower	27.4596	Lower	8.268	Lower	18.7531
Upper	157.5	Upper	32.4596	Upper	8.768	Upper	23.7531

Figure 6.0 Simulation to Set Limits on the Response

Time Zero Limits Versus Product Lifecycle Limits Due to Stability

To set limits for product lifecycle the following procedure is recommended:
1. Determine tolerance intervals or K sigma limits for the time zero data
2. From the stability data determine the rate of change per month or unit of time
3. Use the following equation to determine the product lifecycle limit. Time Zero Specification Limit + Rate*Number of time points. In most cases only one limit is modified due to the direction of change.

Conclusions

Setting limits and acceptance criteria are critical elements of drug development and an important part of the control plan. Transfer functions, tolerance intervals and K sigma

intervals are key methods to make sure our approach to setting specification limits is statistically rigorous, scientifically sound and defendable to regulatory reviewers.

References:

1. ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, March 1999
2. ICH Q8 Pharmaceutical Development, August 2009
3. ICH Q9, Quality Risk Management, June 2006
4. NIST Engineering Handbook www.itl.nist.gov/div898/handbook
5. http://qualitybydesignconsulting.com/tools/index.php