Best Practices for OINDP Pharmaceutical Development Programs Leachables and Extractables

VIII. Quality Control and Specification Setting

PQRI Leachables & Extractables Working Group

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Definition Review

- A *Leachables Study* is a laboratory investigation into the qualitative and quantitative nature of a particular OINDP leachables profile(s) over the proposed shelf-life of the product. Supports:
  - Developing an extractables/leachables correlation
  - Establishment of drug product leachables acceptance criteria.
- *Routine Extractables Testing* is the testing by which OINDP container closure system critical components are qualitatively and quantitatively profiled for extractables, for:
  - Establishing extractables acceptance criteria
  - Release by established acceptance criteria.

Control of Leachables Through Control of Extractables

- Specifications and acceptance criteria are required for leachables profiles in OINDP.
- Implementation of routine leachables testing and specifications/acceptance criteria is a policy matter.
- If extractables/leachables correlations can be established, then leachables specifications/acceptance criteria may be established as "*if tested will comply*".
- Therefore, in the ideal situation leachables can be controlled through routine testing of extractables.

Routine Extractables Testing

Performed on all critical components of OINDP container closure systems with following general goals:

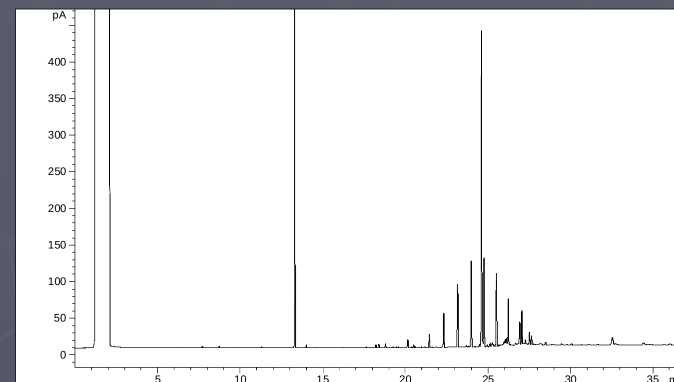
- *To establish extractables acceptance criteria for OINDP critical container closure system components.*
- *To help ensure that the leachables profile in the drug product is maintained within appropriate limits.*
- *To release OINDP container closure system critical components according to established acceptance criteria, which are designed to:*
  - *Confirm the identities and levels of known extractables;*
  - *Detect "unspecified" extractables which could be present as the result of component ingredient changes, manufacturing changes, external contamination, or other causes.*

Recommendations for Routine Extractables Testing

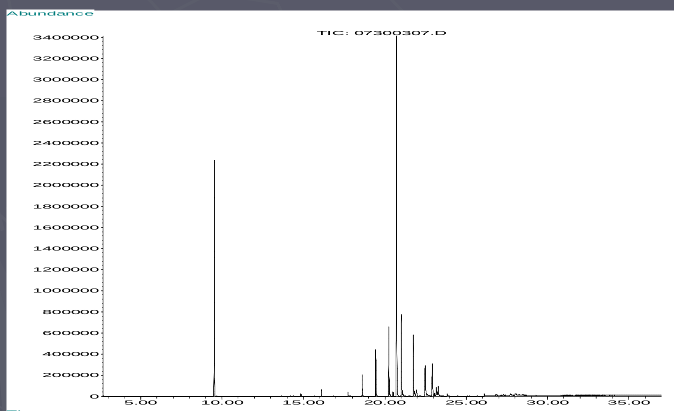
- Analytical methods for Routine Extractables Testing should be based on the analytical technique(s)/method(s) used in the Controlled Extraction Studies. Consider the following:
  - Simplicity relative to R&D methods
  - Ruggedness and robustness
  - Transferability
  - Cost effectiveness

Transition from Extractables Studies Method to Routine QC Extrables Testing

Routine Extractables Method – GC/FID

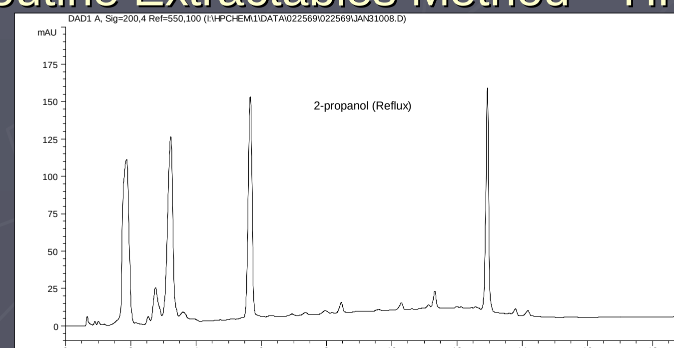


GC/MS Extractables Profile of an Elastomer



Development Method

Routine Extractables Method – HPLC/UV



Quality Control Method(s)

Routine Extractables Testing- Method Development and Validation-References

1. ICH Harominzed Tripartite Guideline, "Text on Validation of Analytical Procedures Q2A", International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
2. ICH Harominzed Tripartite Guideline, "Validation of Analytical Procedures: Methodology Q2B", International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
3. "Reviewer Guidance – Validation of Chromatographic Methods", Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration, November, 1994.
4. "Guidance for Industry – Analytical Procedures and Methods Validation – Chemistry, Manufacturing, and Controls Documentation", *Draft Guidance*, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration, August, 2000.
5. Michael E. Swartz and Ira S. Krull, Analytical Method Development and Validation, Marcel Dekker, Inc., New York, 1997.

Routine Extractables Testing- Method Development and Validation

- Extraction procedures for critical components should be based on the optimized procedures from the quantitative Controlled Extraction Studies
  - Demonstrate asymptotic levels of extractables.
- The linear dynamic range of the analytical method should be established based on levels of extractables anticipated from quantitative *Controlled Extraction Studies*
- The Limit-of-Quantitation of the method should be established with consideration of the appropriate AET.

Routine Extractables Testing- Method Development and Validation (cont.)

- Method validated according to the ICH validation characteristics of a quantitative impurity test,
  - Include: Accuracy, Precision (Repeatability, Intermediate Precision), Specificity, Limit-of-Quantitation (LOQ), Linearity, and Range.
  - System Suitability parameters should be established
  - Robustness should be evaluated
  - *Note that in certain cases it may be appropriate to validate routine extractables methods as "Limit Tests", in which case only Specificity and Limit-of-Detection (LOD) need be considered.*
- Accuracy can be determined through the analysis of spiked samples.
  - Spiking matrix could be an extract taken through the extraction procedure minus the component sample.
  - Spiking levels should be chosen so as to be representative of anticipated extractables levels based on results from quantitative Controlled Extraction Studies.

Specifications and Acceptance Criteria for Leachables

- Leachables specifications should include a fully validated analytical test method.
- Acceptance criteria for leachables should apply over the proposed shelf-life of the drug product, and should include:
  - *Quantitative limits for known drug product leachables monitored during product registration stability studies.*
  - *A quantitative limit for "new" or "unspecified" leachables not detected or monitored during product registration stability studies.*

Specifications and Acceptance Criteria for Leachables

- *Quantitative acceptance criteria should be based on safety considerations as outlined in the 'L&E Best Practices'*
  - *Actual leachables levels, and trends in leachables levels, observed over time and across various storage conditions and drug product orientations during product registration stability studies should be considered.*
- *Ability to consistently meet should be established with appropriate statistical analysis.*

Specifications and Acceptance Criteria for Leachables

- *Comprehensive correlation should obviate the need for routine implementation of drug product leachables specifications and acceptance criteria, assuming:*
  - *Adequate information from critical component suppliers*
  - *Understanding and control of critical component fabrication*
  - *Controlled Extraction Studies on critical components.*
  - *Validated leachables methods and a Leachables Study.*
  - *Validated Routine Extractables Testing methods and database of critical component extractables profiles.*
  - *Appropriate specifications and acceptance criteria for extractables*

Specifications and Acceptance Criteria for Extractables

- Routine Extractables Testing should be performed on OINDP critical components prior to drug product manufacture.
- Critical components should be released to drug product manufacture based on defined specifications and acceptance criteria established through:
  - Understanding of critical component composition(s), ingredients, and compounding/fabrication processes.
  - Comprehensive Controlled Extraction Studies.
  - A significant database of extractables profiles obtained with validated Routine Extractables Testing methods.
  - A complete leachables/extractables correlation.

Specifications and Acceptance Criteria for Extractables

- Acceptance criteria for OINDP critical component extractables can include the following:
  - *Confirmation of extractables identified in Controlled Extraction Studies.*
  - *Quantitative limits for extractables identified in Controlled Extraction Studies.*
  - *A quantitative limit for "new" or " unspecified" extractables not detected during Controlled Extraction Studies.*

Establishing Specifications: Widgets vs. Pills

- Rest of World (Planes, Trains & Automobiles...)
  - Known requirements that must be met to insure product performance
  - Establish that process is capable of meeting requirements
- Pharmaceuticals
  - Vaguely known requirements (vs product performance)
  - Establish requirements from vaguely known process capabilities

Statistical Tools Related to Specifications

- Process Capability & Performance Analysis
  - Statistical evaluation of process variability with respect to limits
  - Typically includes both process and measurement variability
- Operating Characteristic Curves
  - Statistical evaluation of decision making process related to an individual test
  - Considers influence of different test structures: numbers of samples, average vs. individuals, tiered testing…

Types of Quality Inspections

- Inspection by Attributes
  - Defect testing (pass/fail by unit)

    Visual inspection of containers for foreign material or defects

    Spray test of MDIs
- Inspection by Variables
  - Estimation of Batch Parameters (central tendency, variability)

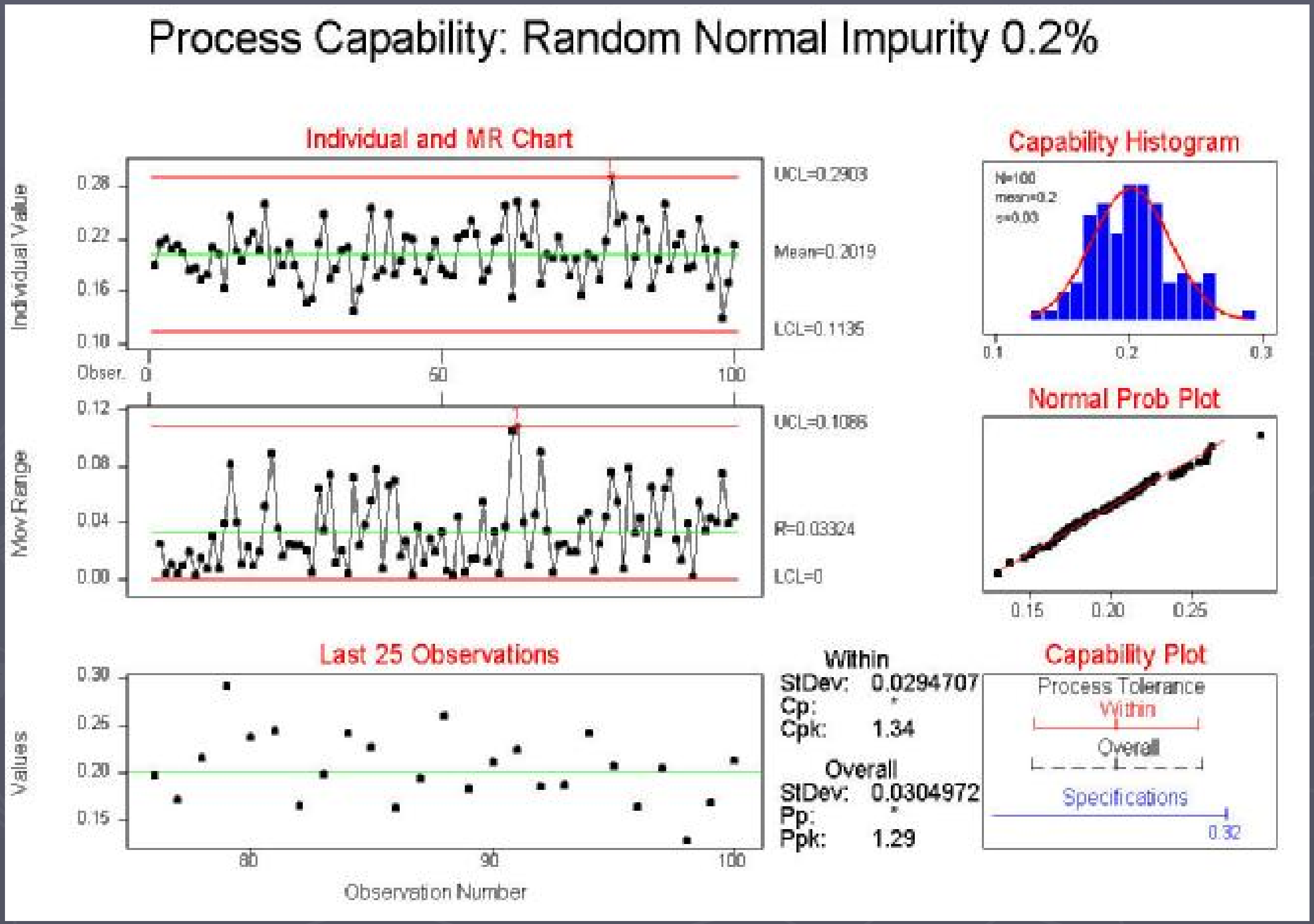
    HPLC Assay of tablets for active ingredient

    Delivered Dose Uniformity of an MDI

    Content Uniformity of a tablet

    Leachable/extractable testing

What we would like to have to establish/verify acceptance criteria:



What we typically have to establish acceptance criteria:

Impurity X

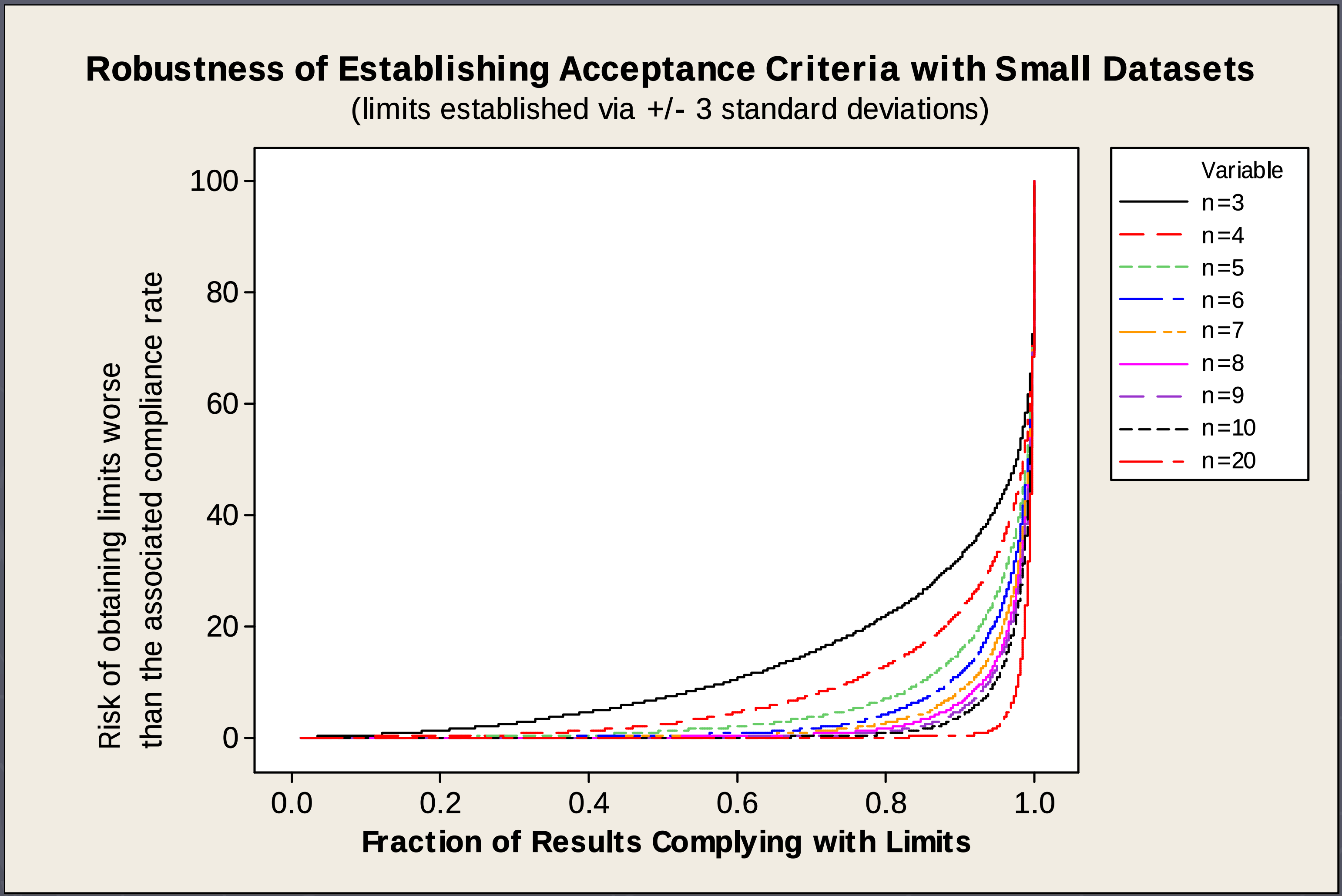
0.24

0.07

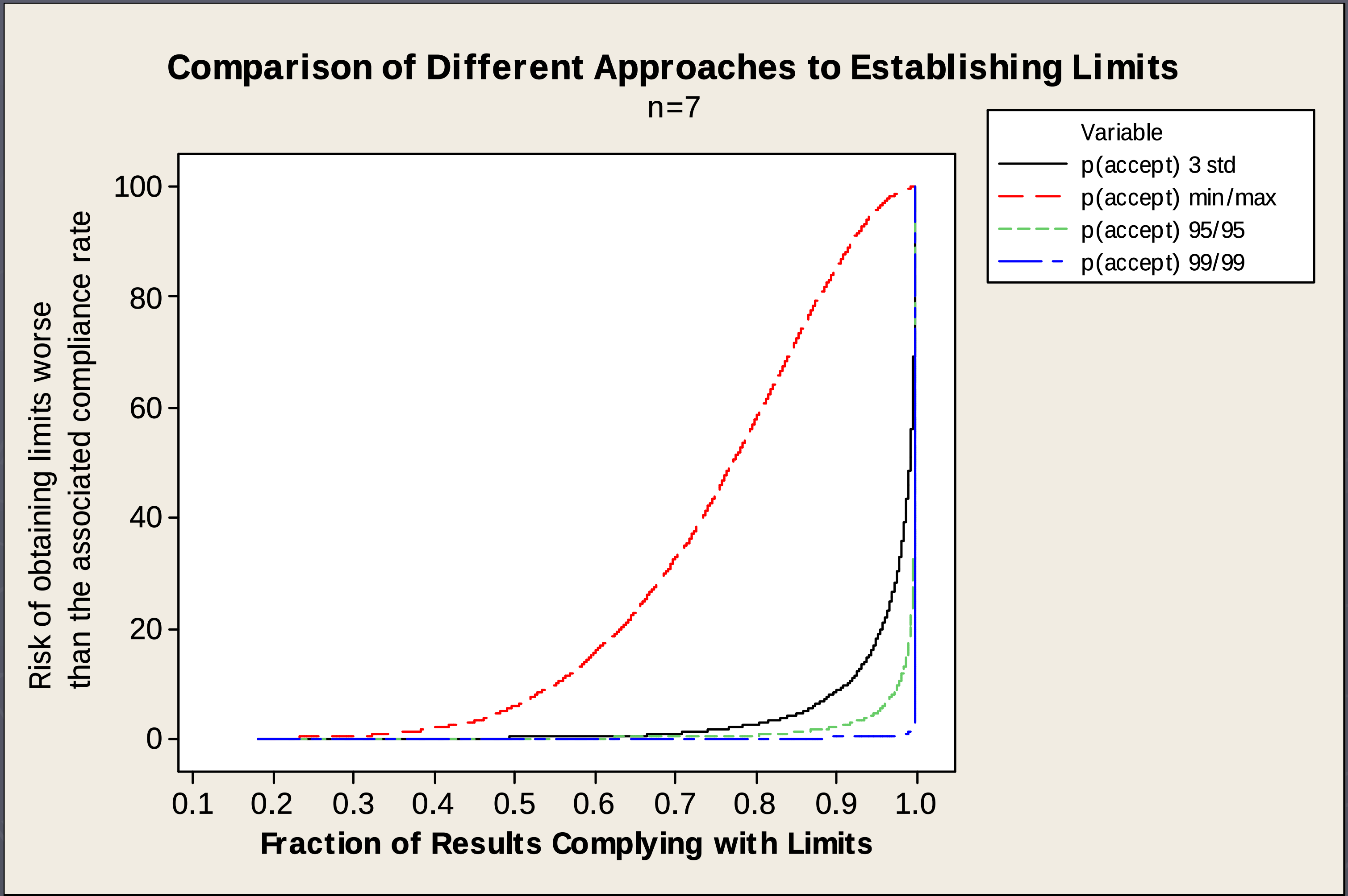
0.15

ND

Performance of Limits Established with Small Datasets



Comparison of Different Approaches to Setting Limits



Process Capability & Performance

- Process Capability: Statistical comparison of inherent process variability (*common cause* variability only) to some limits. Generally, represents the best possible performance.
- Process Performance: Statistical comparison of the total observed variability to some limits. May include *special cause* variability.

Process Capability

- Several different 'Capability Indices' exist
- Designed to show whether process+measurement are capable of meeting limits

$$Cp=(USL-LSL)/6\sigma_w$$

$$Cpk=Min\{[(USL-Avg)/3\sigma_w],[(Avg-LSL)/\ 3\sigma_w]\}$$

- Minimum Cpk of 1.33 expected for new process
- Cp ~ Cpk when process is 'centered'
- Above is for two-sided limit, for a one-sided limit Cp is meaningless and Cpk considers only the range to the specified limit

Process Performance

- Several different 'Performance Indices' exist
- Designed to show process+measurement performance relative to limits

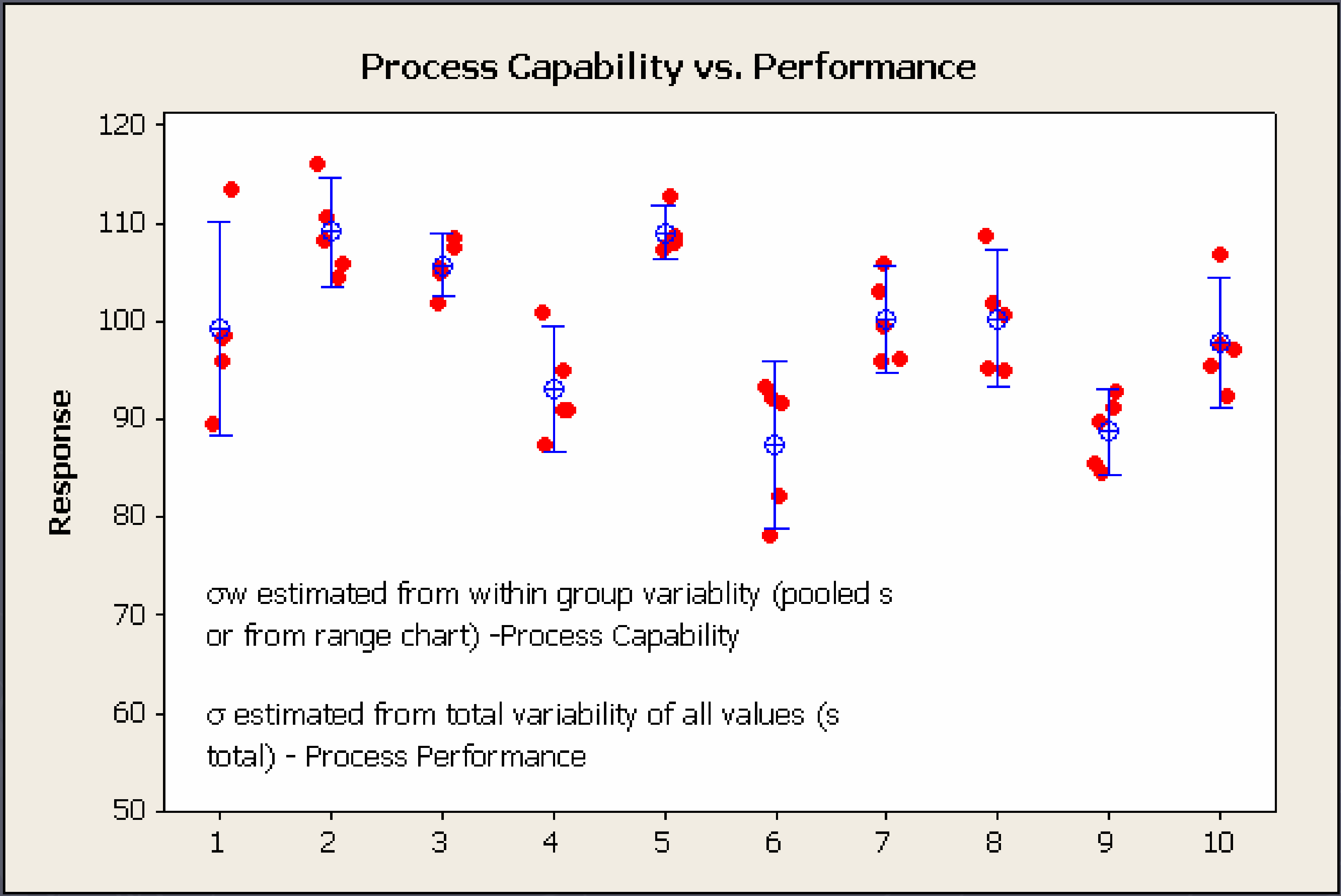
$$Pp=(USL-LSL)/6\sigma$$

$$Ppk=Min\{[(USL-Avg)/3\sigma],[(Avg-LSL)/\ 3\sigma]\}$$

- Minimum Ppk of 1.33 expected for new process
- Ppk ~ Cpk when no 'special cause' source of error
- Above is for two-sided limit, for a one-sided limit Pp is meaningless and Ppk considers only the range to the specified limit

Example Cp,Cpk,Pp,Ppk

- Consider a set of extractable data collected as follows:
  - 5 gaskets where sampled from each of 10 lots of gaskets
  - The level of extractable "A" was determined for all 50 samples
  - Based on tox information and a leachables correlation an upper limit of 120 ppm is being considered
  - Normally an extractable limit is a one-sided limit, but for sake of this example suppose we are also interested in a lower limit i.e. 80 ppm (this allows calculation of Cp & Pp which are meaningless for a one-sided limit)
- Can the gasket manufacturing process support this limit?
- What else can we conclude about the gasket process?



Process Capability vs. Performance
Response
120
110
100
90
80
70
60
50
1
2
3
4
5
6
7
8
9
10
σw estimated from within group variablity (pooled s
or from range chart) -Process Capability
σ estimated from total variability of all values (s
total) - Process Performance

Calculating Cp, Cpk, Pp, Ppk

Using actual numbers from previous figure:

		1	2	3	4	5	6	7	8	9	10
		98.7	104.6	108.6	91.0	112.8	82.1	99.5	108.8	89.8	92.5
		96.0	110.7	105.0	87.5	108.2	93.3	96.3	95.4	92.8	97.1
		98.3	106.0	101.9	95.1	107.4	78.2	106.0	100.8	91.2	95.4
		89.6	116.1	107.6	91.1	108.7	92.2	95.9	94.9	85.5	106.8
		113.5	108.4	105.5	101.1	108.1	91.7	103.2	101.8	84.5	97.5
	Std Dev	8.8	4.5	2.6	5.2	2.2	6.9	4.4	5.7	3.6	5.4
	Range	23.8	11.5	6.7	13.6	5.4	15.1	10.1	13.9	8.3	14.3
	Std Dev (range)	10.2	4.9	2.9	5.8	2.3	6.5	4.3	6.0	3.5	6.1
										Overall Mean	99.1
										Overall Std Dev	8.72
										Within Std Dev	5.25

Note: Std Dev (s) can be estimated from range (R) by $s=R/d_2$

d_2 is a tabulated by n; for n=5, d_2=2.33

Calculating Cp, Cpk, Pp, Ppk

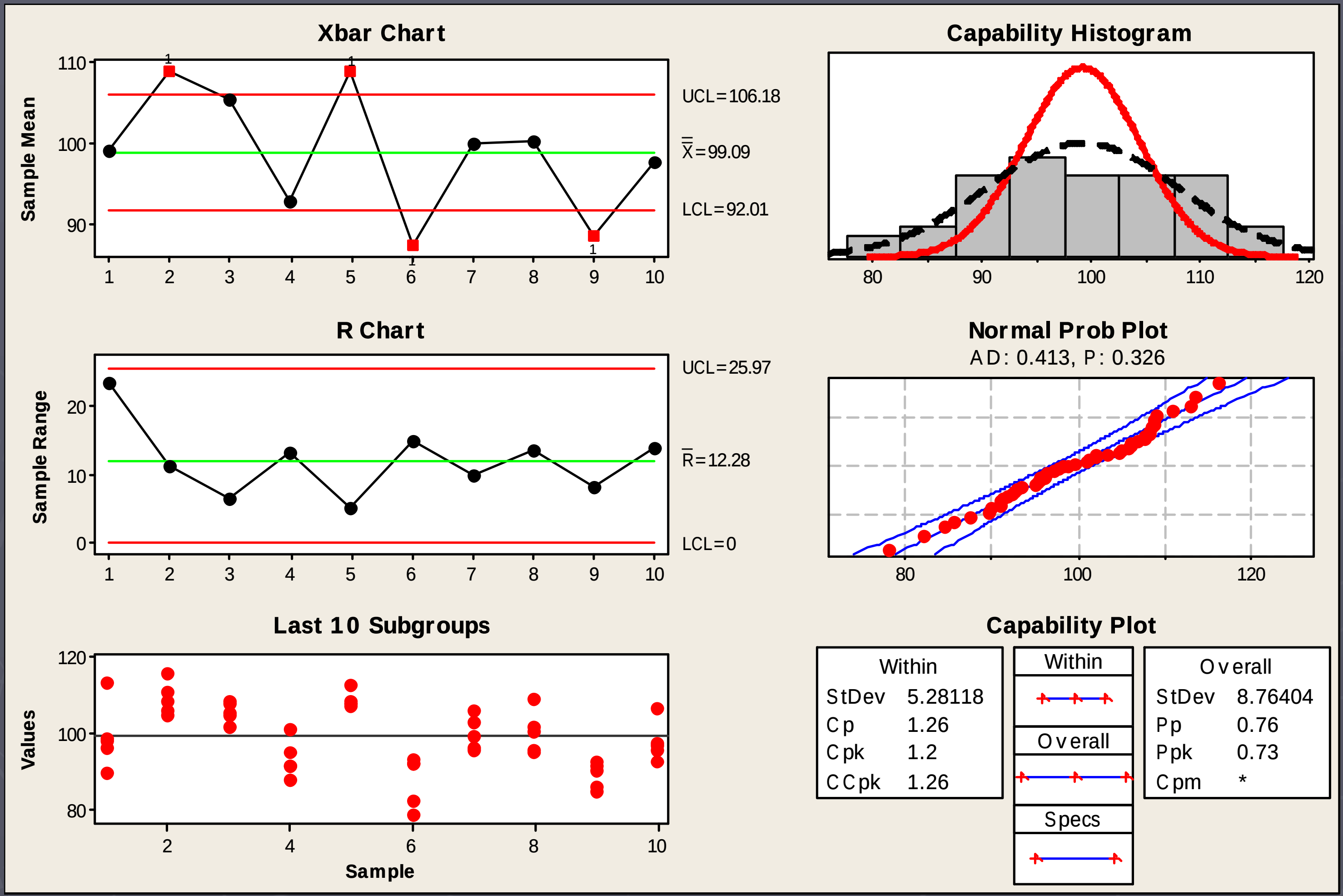
Cp=(120-80)/(6)(5.25)= 1.27

Cpk=min[(120-99.1)/(3)(5.25)],
[(99.1-80)/(3)(5.25)]= 1.21

Pp=(120-80)/(6)(8.72)= 0.76

Ppk=min[(120-99.1)/(3)(8.72)],
[(99.1-80)/(3)(8.72)]= 0.73

Process Capability/Performance using MINITAB®

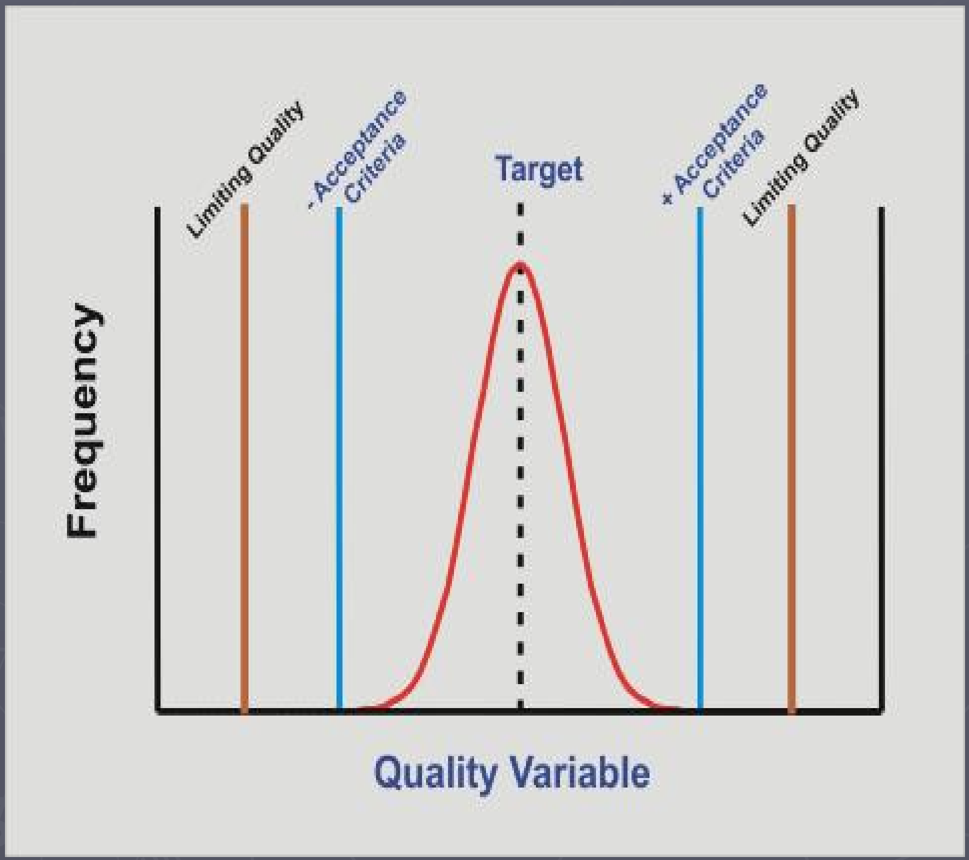


Designing & Evaluating Test Structures: Operating Characteristic Curves

Quality Decisions: Possible Outcomes and Consequences

Decision	True Situation: Batch is of Acceptable Quality	True Situation: Batch is not of Acceptable Quality
Accept Batch	**Correct Decision**	**Type II error (β) (‘consumer’s risk’)**
Reject Batch	**Type I error (α) (‘producer’s risk’)**	**Correct Decision**

Quality Standards vs. Acceptance Criteria



Quality Standard:

- All units must have an assay greater than 95%

Test Acceptance Criteria:

- Assay of 2 of 2 Samples must be between 98-102%

Quality standard should drive acceptance criteria and test structure

OCCs used in this context

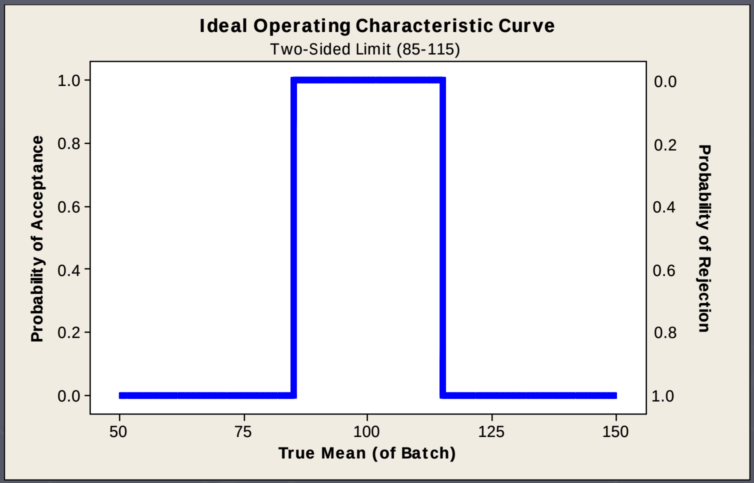
Operating Characteristic Curves

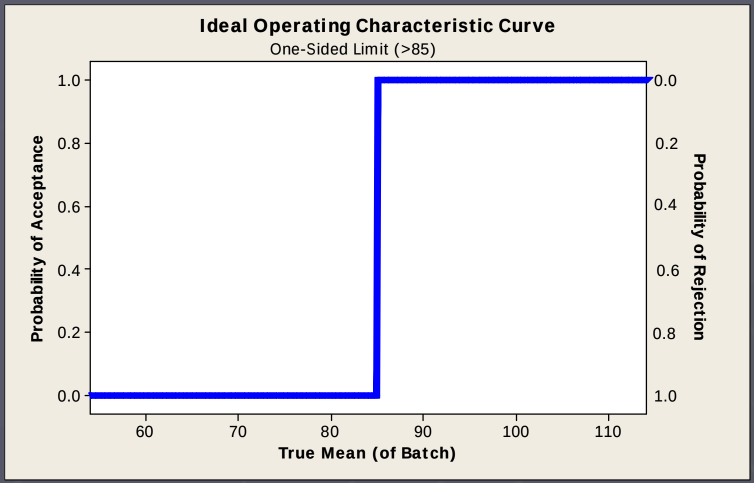
- Used to characterize the statistical qualities of the decision making process associated with a particular test's structure/form
  - Test structure/form includes: numbers of samples, limits, tiers, decision process flow, quaniti(es) compared to limit
- Comment on the ability of the test structure to discriminate between acceptable and unacceptable 'batches'
- Allows estimation of type I & II error rates
  - risk of failing an acceptable batch
  - risk of passing an unacceptable batch

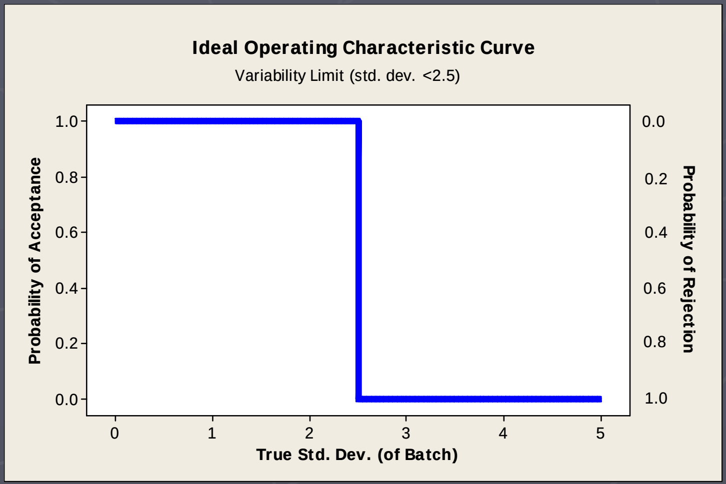
Operating Characteristic Curves

- Plot of the probability of acceptance (or rejection) vs. the quality variable
  - P(accept) vs. true batch mean
  - P(accept) vs. true batch standard deviation
  - P(accept) vs. true % defects
- Constructed using the appropriate cumulative density probability distribution

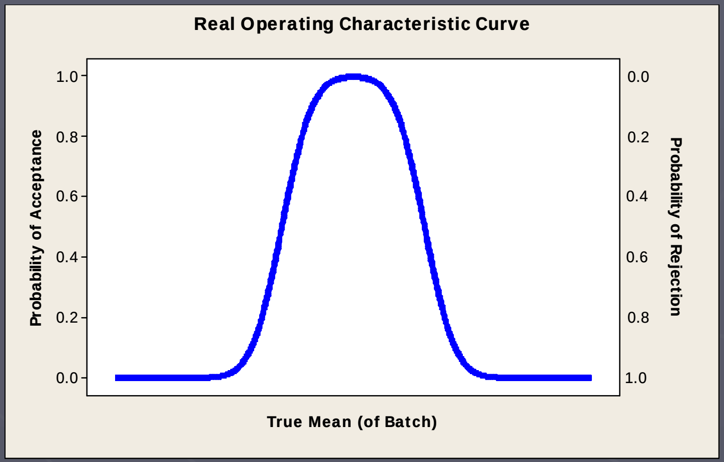
Ideal OC Curves

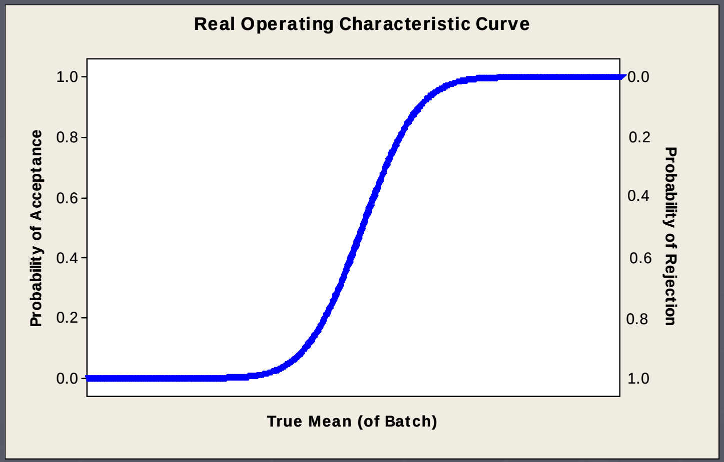


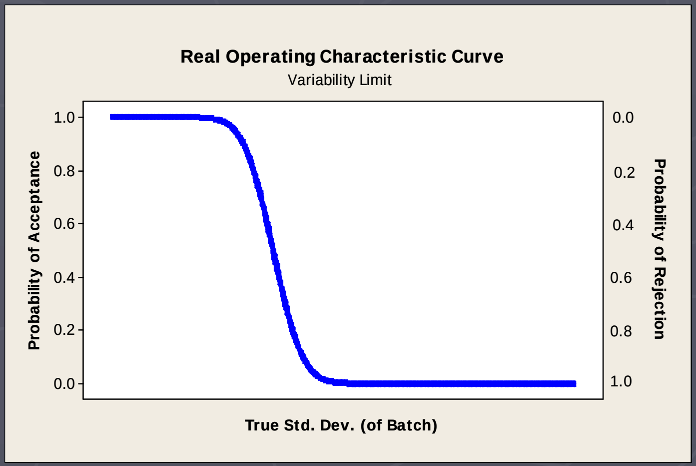


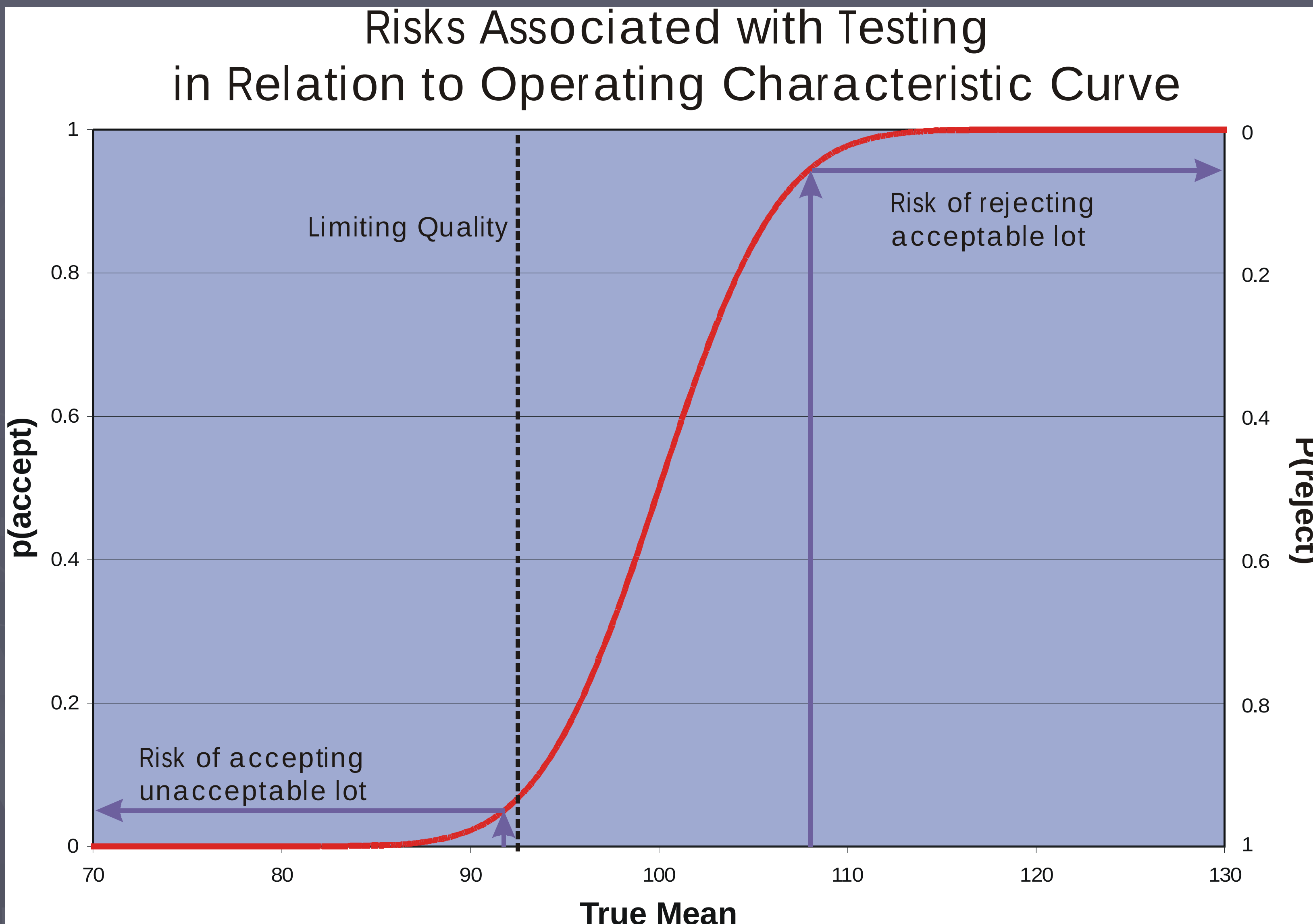


Typical OC Curves








Risks Associated with Testing
in Relation to Operating Characteristic Curve
Limiting Quality
Risk of rejecting
acceptable lot
Risk of accepting
unacceptable lot
p(accept)
P(reject)
True Mean
1
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1
70
80
90
100
110
120
130

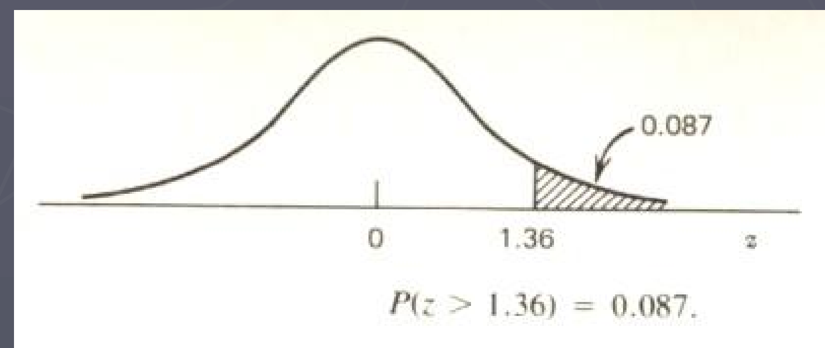
Process for Constructing OC Curves: p(accept) vs. Mean

- Need model probability distribution for individual measurements
- Need estimate of standard deviation
  - Curve is for an assumed standard deviation of the individual measurements
- Calculate probability to accept for a given value of the mean from the appropriate cumulative density probability distribution based on the test construct
- Alternatively can estimate through numeric approach
- Repeat over range of means of interest

Example Calculations OC Curve: Sample mean compared to a two-sided limit

- Normal Distribution:

$$f(y) = \frac{1}{s\sqrt{2p}} e^{-(y-m)^2/2s^2}$$



- Need areas under distribution
- No analytical solution
- Numeric approaches used leading to tabulations of cdf: cumulative density function

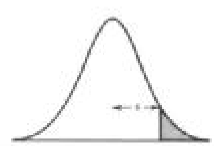


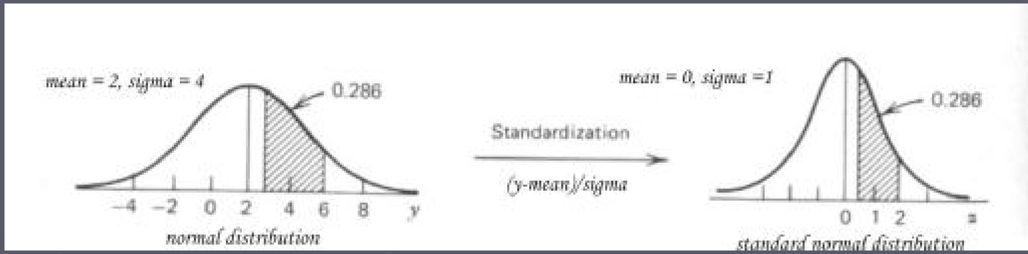
TABLE A. Tail area of unit normal distribution

z	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
0.0	0.5000	0.4960	0.4920	0.4880	0.4840	0.4801	0.4761	0.4721	0.4681	0.4641
0.1	0.4602	0.4562	0.4522	0.4483	0.4443	0.4404	0.4364	0.4325	0.4286	0.4247
0.2	0.4207	0.4168	0.4129	0.4090	0.4052	0.4013	0.3974	0.3936	0.3897	0.3859
0.3	0.3821	0.3783	0.3745	0.3707	0.3669	0.3632	0.3594	0.3557	0.3520	0.3483
0.4	0.3446	0.3409	0.3372	0.3336	0.3300	0.3264	0.3228	0.3192	0.3156	0.3121
0.5	0.3085	0.3050	0.3015	0.2981	0.2946	0.2912	0.2877	0.2843	0.2810	0.2776

Example Calculations OC Curve: Sample mean compared to a two-sided limit

- For each point on the OC Curve, need to calculate area under distribution (μ,σ) between limits, i.e. prob(accept) for a given value of the mean (μ)
- Consider two sided limits of 95-105 and σ=2
  - σ: standard deviation of sample means
  - This σ related to σ of individual measurements by a factor of $1/\sqrt{n}$

Example Calculations OC Curve: Sample mean compared to a two-sided limit



- For example, to calculate p(accept) at μ=99 first convert limits to standardized units (z)
- (95-99)/2 = -2; (105-99)/2 = 3
- From tabulation of CDF or stat program:
  - Area below z=-2 is 0.02275
  - Area above z=3 is 0.00135
  - Area between z=-2 to z=3 is

    1-0.02275-0.00135=0.97590

Example Calculations OC Curve: n of n compared to a two-sided limit

- Follow above procedure to calculate the prob(accept) a single value.
- The probability to accept n of n values is:

$$P(accept_1)^n$$

- If the previous example instead required 3 of 3 results to be within 95-105, then

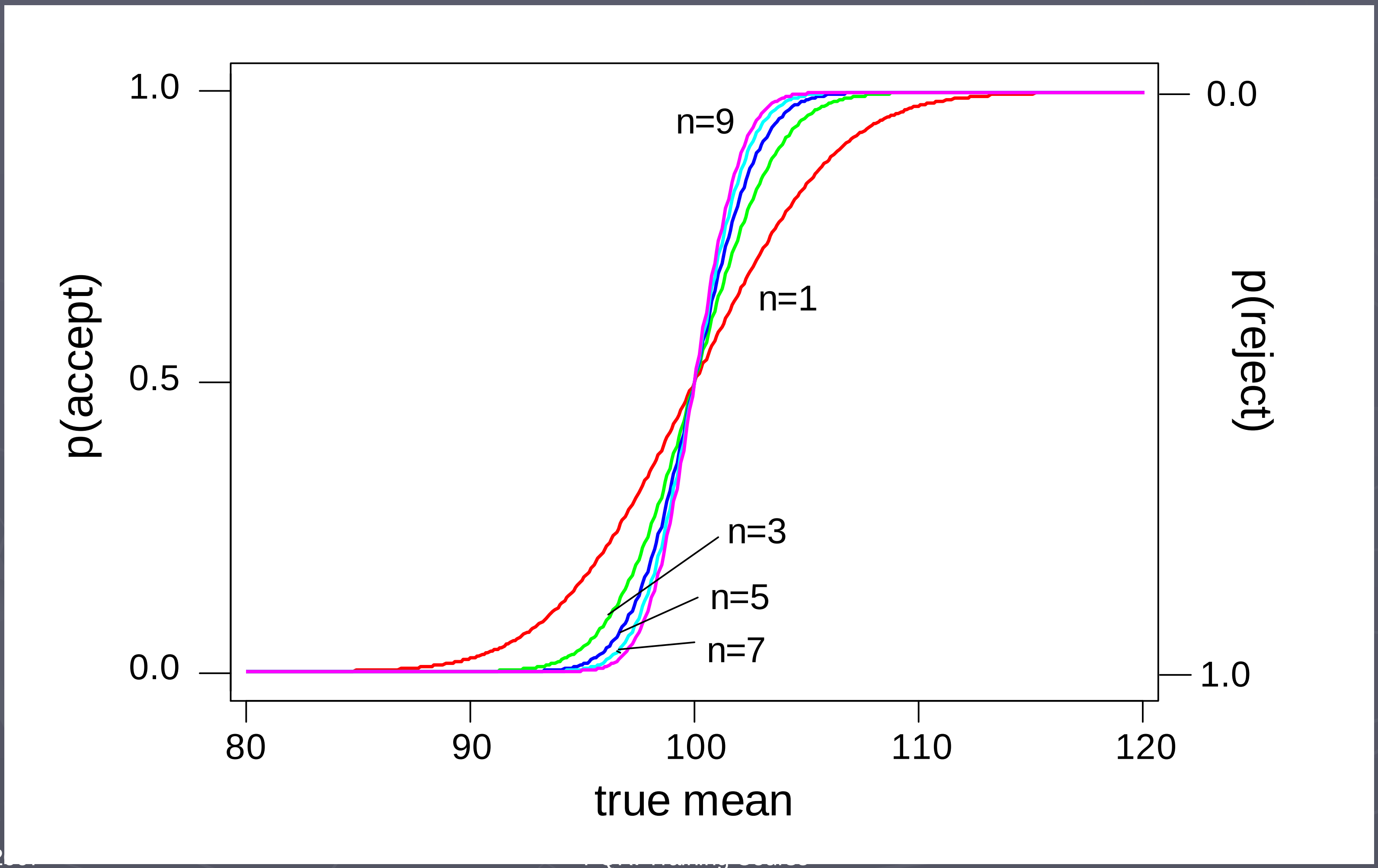
$$P(accept)=(0.97590)^3=0.92943$$

Influence of Different Test Designs on the OC Curve

- Tests Designed to Control Mean
  - Vary n, set requirement on sample mean
  - Vary n, set requirement on individual values
  - Influence of acceptance criteria

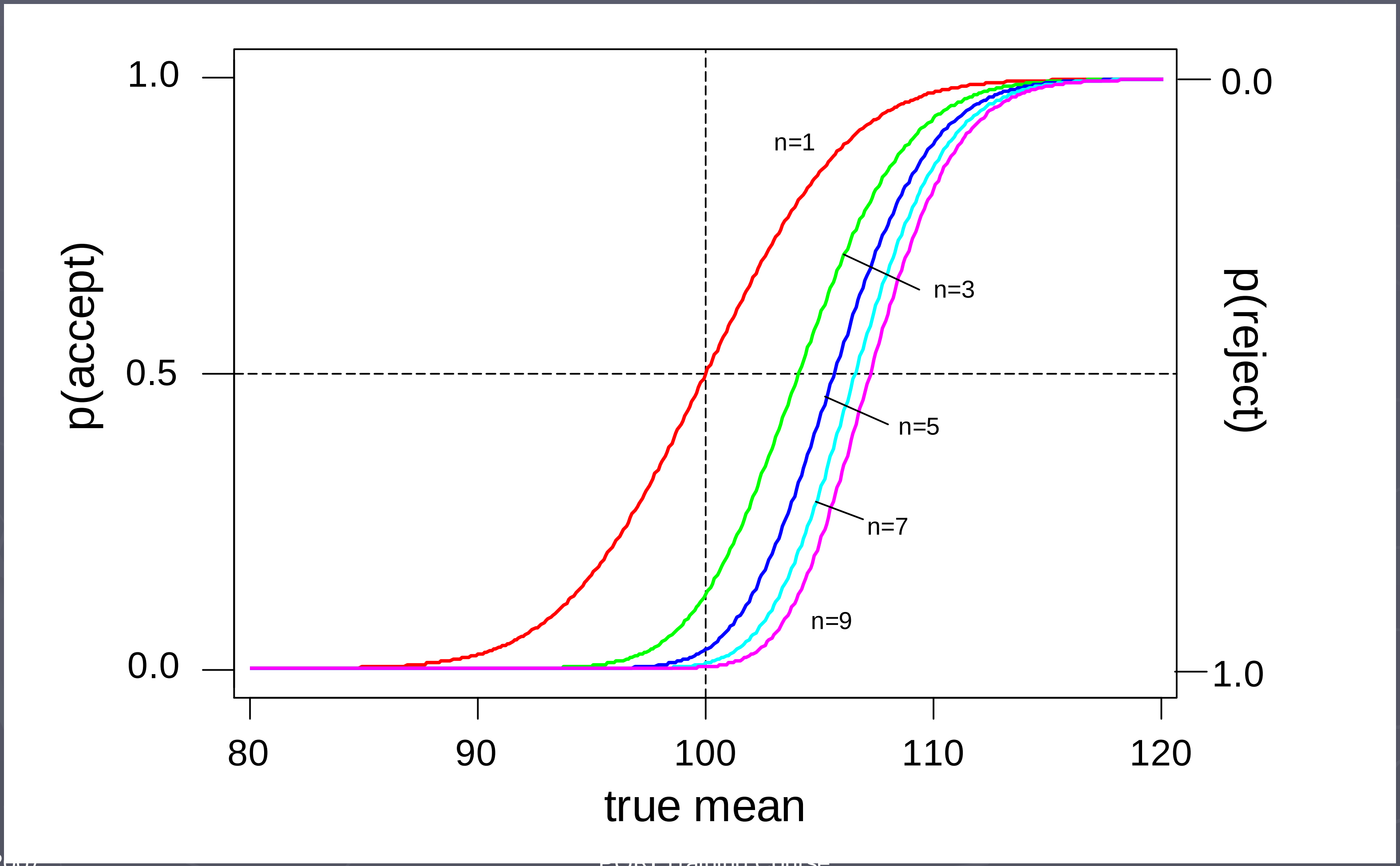
Control on Batch Mean
Improvement in OC Curve as Sample Size Increases

Acceptance Criteria: Sample Mean > 100

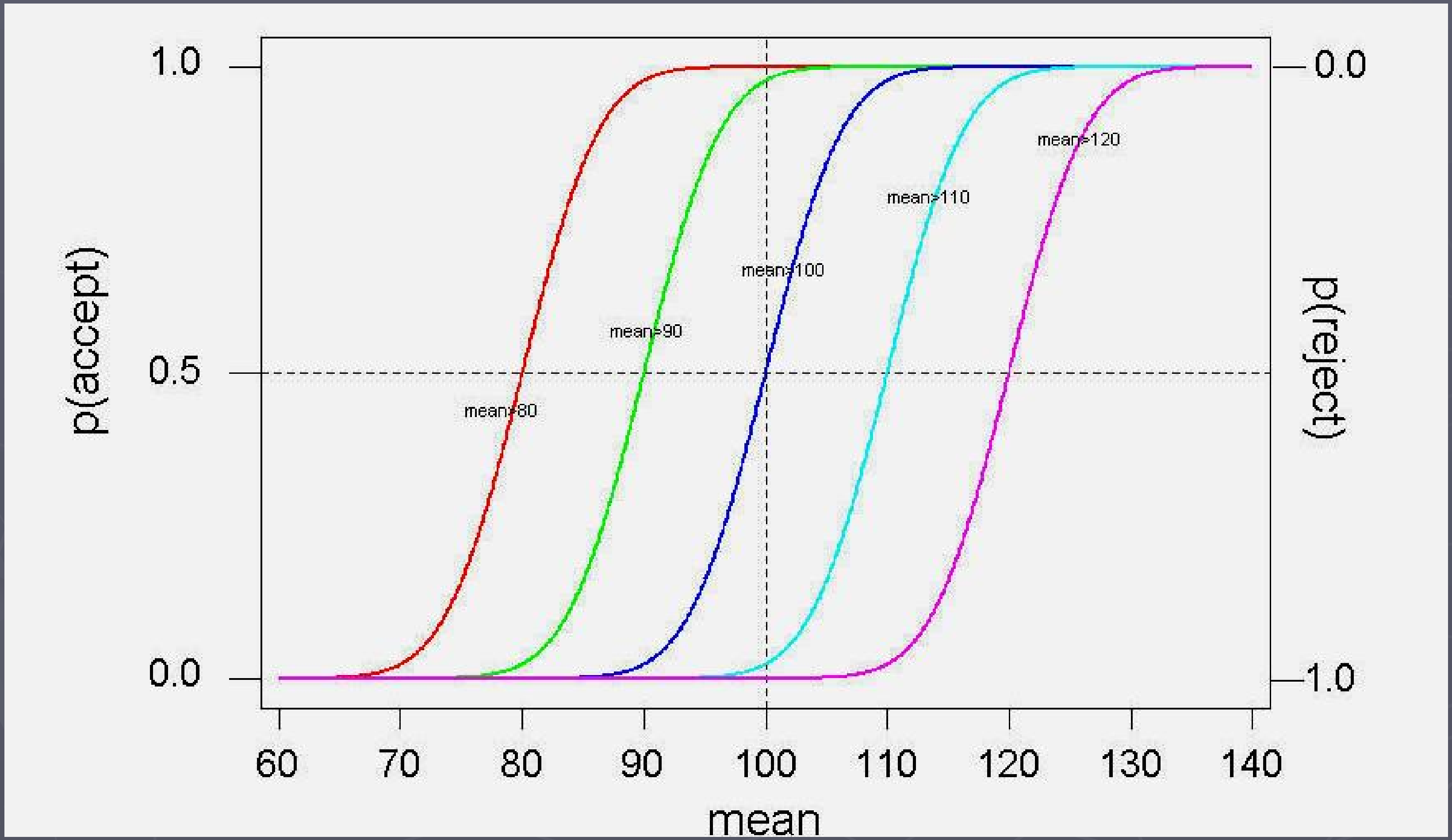


Control on Batch Mean
Effect on OC Curve as Sample Size Increases
for n of n Requirement

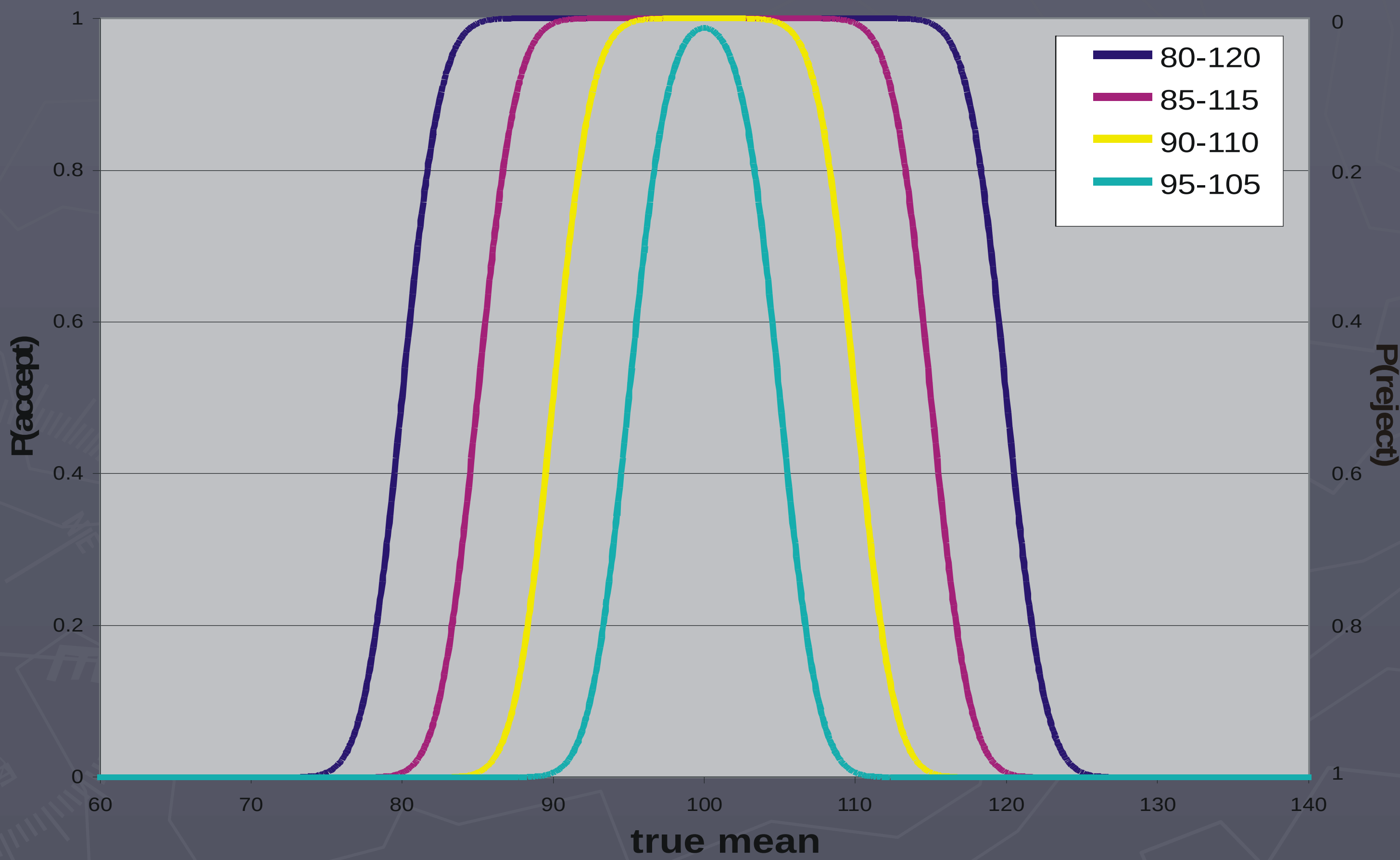
Acceptance Criteria: n of n > 100



Relationship of OC Curve to Specification Limits (one sided)



Relationship of OC Curve to Specification Limits (two sided)



Conclusions & Final Thoughts

- Appropriate L&E testing schemes should reflect:
  - In-depth understanding of component composition and the L&E characteristics of the product/component
  - Thoughtful selection of critical tests
  - Robust validated methods
  - Statistical design and evaluation of tests and acceptance criteria