Confidence – Critical to Batch Release

Application of **ASTM E2709**

Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure

and Its Relationship to USP Standards

Product Research

- Stability Failures
  - Research into dissolution data provided in application annual reports
  - Data indicated periodic specification failures with no degradation trend
  - No correlation of failures with age of the product

Pattern

- Large batch sizes
- Small sample sizes for testing
- Periodic test failures

- This is a pattern expected for a process with a systematic variable output

Plausible Explanation

- The batches are released with samples too small for characterizing variability.
- With time, the stability data adds information and reveals the variability of initial production.
- This variability results in occasional failures of dissolution on stability.
- Dissolution is sensitive to this variability because it is a test of single dosage units.

Supporting Information

- This variability is expected to cause occasional failing batches.
  - Infrequent
  - Lack of clear cause
  - A pattern reliable enough to consider it a business cost

Standard History

- ASTM E2709 was published in September 2009 through committee E11 - Quality and Statistics
    - This methodology computes, at a prescribed confidence level, a lower bound on the probability of passing a lot evaluation/acceptance procedure
- A work item was approved and opened in July 2010 (Specific to USP Uniformity of Dosage Units) through committee E55 – Manufacture of Pharmaceuticals
    - This practice computes, at a prescribed confidence level, a lower bound on the probability of passing the USP Uniformity of Dosage Units test
- Future Plans
  – Develop pharmaceutical specific standards within ASTM E55 that are applicable to numerous USP standards (e.g. Dissolution)

Background

- Developed in Mid 80's by James Bergum (1)
  - Shows Specific Quality Attributes will meet associated Market Standards (USP)
  - Valid for any processing step where an acceptance criteria is specified
- The procedure (E2709) computes, at a prescribed confidence level, a lower bound on the probability of passing USP standards and/or any other specification/acceptance criteria.
  - An acceptance limit table can also be generated that states what the maximum RSD values are for each specific mean given the pre-specified sample size, confidence and probability.

(1) Bergum, J.S., "Constructing Acceptance Limits for Multiple Stage Tests". *Drug Development and Industrial Pharmacy,* Vol 16, No 14, 1990, pp.2153-2166.

Statistical Power

- The ability of a method/test to detect an actual effect or difference
- The Journal of Pharmaceutical Innovation published an article in March 2009 (2)
- Simulation study was performed to investigate the statistical power of the revised USP<905> and E2709's acceptance limits
- Conclusions
  - "USP<905> is relatively insensitive to detecting non-conforming material"
    - "Lots were not consistently rejected until defect>20%"
  - "E2709 was highly effective in identifying nonconforming material"
    - "Did not make an incorrect inference in over 11,000 simulation trials"

(2)Lunney, P.D., Anderson, C.A., "Investigation of the Statistical Power of the Content Uniformity Tests Using Simulation Studies", Journal of Pharmaceutical Innovation, pp 24-35, 13March2009.

Justification for Standard

- Provides high confidence that batch meets regulatory standard
- Provides more confidence with increased sample size.
  - Manufacturer's may want to sample more than the USP standards require, but still want to make some sort of inference regarding the market standard.
- Tied directly to regulatory requirements.
  - 211.110(a) – Examination and testing of samples shall assure that the drug product and in-process material conform to specifications
  - 211.160(b) – Establishment of scientifically sound and appropriate specifications
  - 211.165(d) – Sampling plan must result in statistical confidence for release/distribution
- Meets expectations set forth by the Draft Validation Guidance
  - Detecting process drift
  - Inter/Intra batch variability characterization
  - ↑Sampling → ↑Process Knowledge → ↓Risk

Final Statistical Statement

- Probability that a future sample pass the USP standard
- Example: With 99% confidence, a future standard sample taken from the batch has greater than a 99% chance of passing the USP market standard.

Acceptance Limit Table for USP Content Uniformity Test

99% Confidence Interval, 99% Probability
n=30

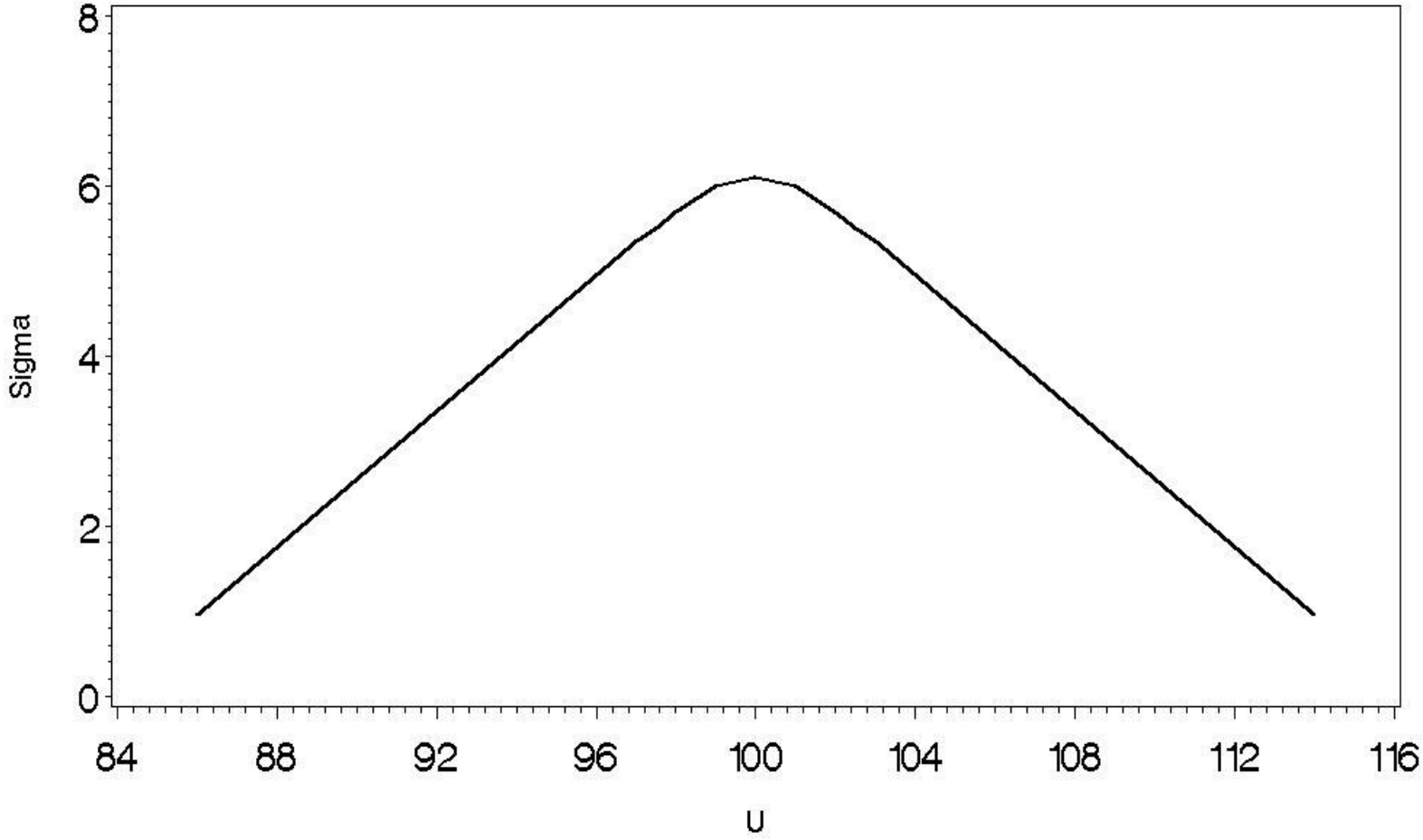
Sample Mean	RSD (%)
95	2.50
97.5	2.97
100	3.40
102.5	2.82
105	2.26

Meeting Relative Standard Deviation (RSD) Limit assures, with 99% confidence, that a future standard sample taken from the batch has greater than a 99% chance of passing the USP Content Uniformity test.

Message

- As the measured average value approaches the target
  - More variability can be tolerated
  - More assurance we have of

USP UDU Test
95% Lower Bound Contour



Strategy – Part 1

1. Select Testing Standard
2. Assume probability distribution for individual observations (ex: Normal with parameters μ (Mu) & σ (Sigma))
3. Assuming known distribution parameters, mathematically derive the Lower Probability Bound for each stage. This may also be done by simulation. (Note: Each stage may have multiple criteria!) – This is the hard part!
4. Lower probability bound for overall test is the maximum of the individual stage lower bounds

Example – USP UDU Test

- **Stage 1**
  - Collect random sample of 10 units from lot
  - Express results as percent of target
  - **Criteria**
    - Acceptance Value: $|M - X| + 2.4s \leq 15\%$
    - Otherwise, continue to stage 2
- **Stage 2**
  - Collect an additional 20 units from lot
  - Express results as percent of target
  - **Criteria**
    - Pass if
      - Acceptance Value: $|M - X| + 2.0s <= 15\%$
      - All 30 individual results are between 75% and 125% Target
    - Otherwise, fail test.

Simulation with Calculation

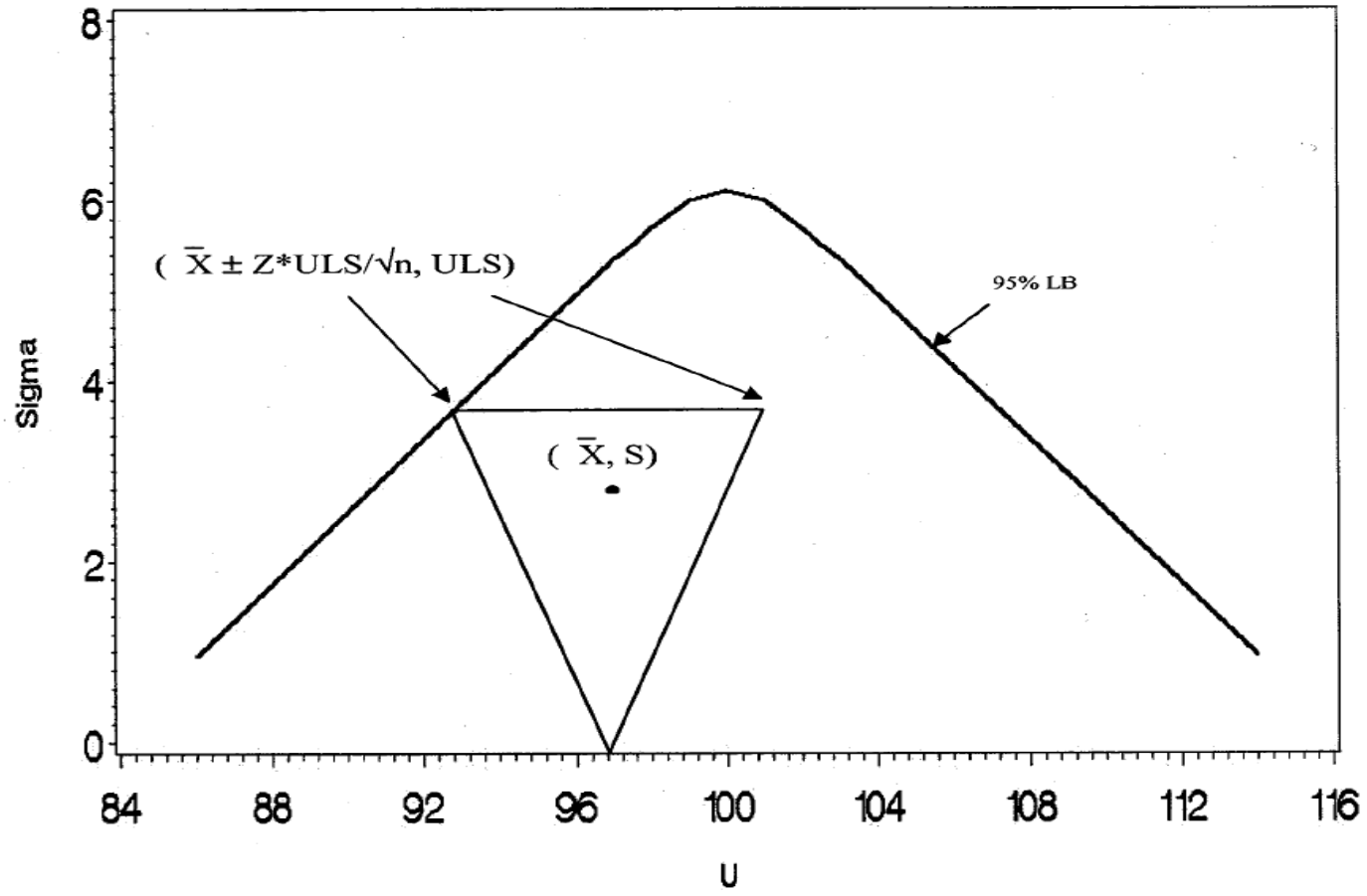
Table 2
Simulated (SIM) vs Lower Bound (LB) Probabilities of Passing CU Test

Population Mean μ		Population Standard Deviation σ					
		1	2	3	4	5	6
88	LB	1.000	0.800	0.093	0.024	0.009	0.004
	SIM	1.000	0.836	0.133	0.026	0.009	0.004
92	LB	1.000	1.000	0.995	0.674	0.162	0.072
	SIM	1.000	1.000	0.996	0.729	0.278	0.094
96	LB	1.000	1.000	1.000	1.000	0.944	0.610
	SIM	1.000	1.000	1.000	1.000	0.955	0.686
100	LB	1.000	1.000	1.000	1.000	1.000	0.964
	SIM	1.000	1.000	1.000	1.000	1.000	0.972
104	LB	1.000	1.000	1.000	1.000	0.944	0.610
	SIM	1.000	1.000	1.000	1.000	0.956	0.688
108	LB	1.000	1.000	0.995	0.674	0.162	0.072
	SIM	1.000	1.000	0.996	0.730	0.276	0.096
112	LB	1.000	0.800	0.093	0.024	0.009	0.004
	SIM	1.000	0.837	0.133	0.026	0.009	0.004

Strategy – Part 2

5. Select Sampling Plan (1 or 2).
6. Construct confidence interval for the sample that was taken based on user defined confidence level.
7. It must fall completely below the specified lower bound.
8. If the confidence interval is contained within the lower bound, then you meet the assurance requirements of the standard.
9. An acceptance limit table can be generated by finding the largest standard deviation for a fixed sample mean such that the resulting confidence interval remains below the pre-specified lower bound.

USP UDU Test Lower Bound with Confidence Interval



Picking a "n" for E2709 Application

- Manufacturers should not use compendial specified sample size
- Lot size should not dictate how big or small the sample size is.
- Sample size should be based upon process average and variability estimates.
  - Confidence bounds around estimates?
- The larger the sample size that is chosen, the larger will be the acceptance region.

Acceptance Limits

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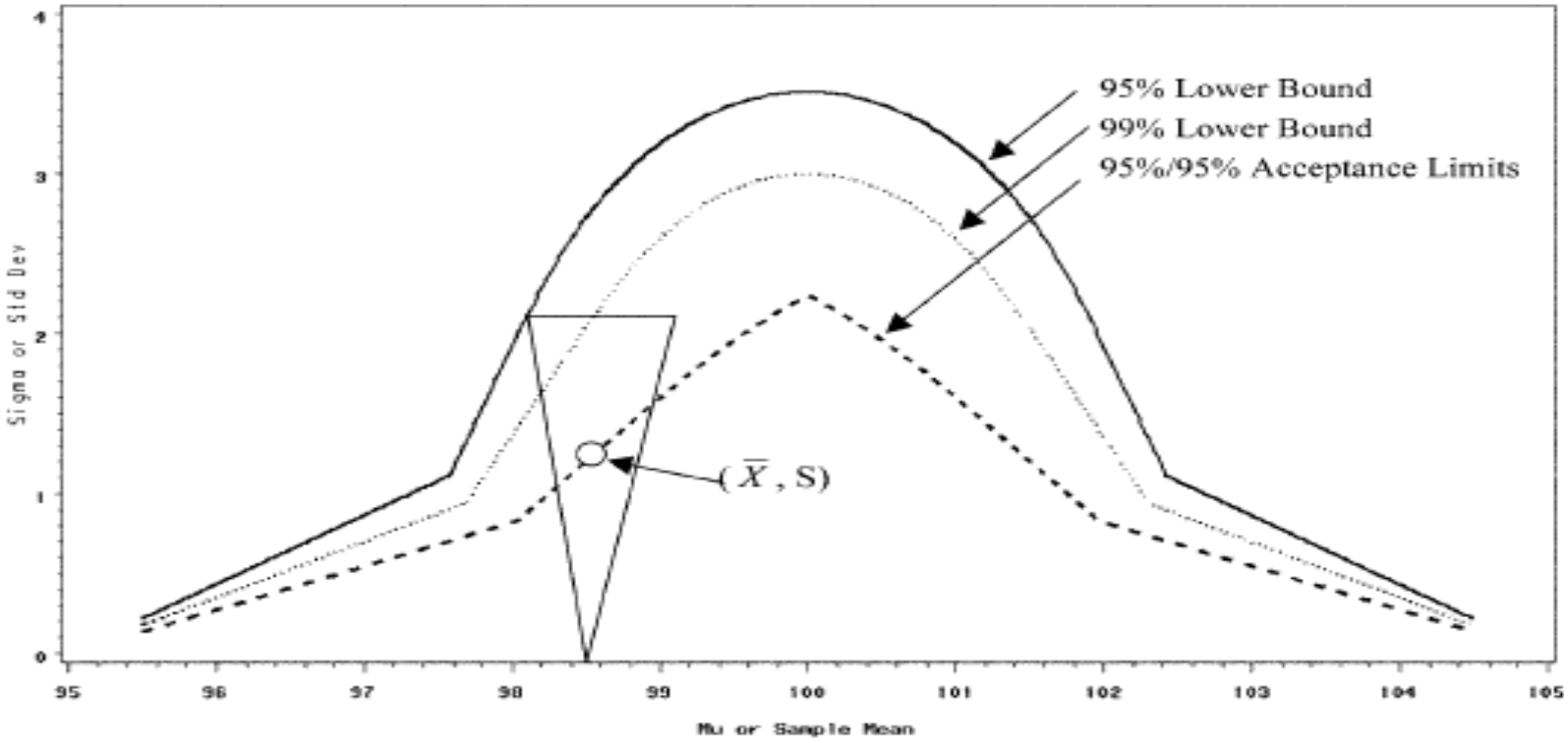


FIG. 1 Acceptance Limit Contour Showing a Simultaneous Confidence Interval With 95% and 99% Lower Bound Contours

Acceptance Limit Table for Multiple Sample Sizes - UDU

Acceptance Limits for Content Uniformity
Sampling Plan 1
Target=100, Lower Bound=95, Confidence Level=95

Sample Size	10	30	45	60	90	120	150	1000
Mean								
85.1	0.32	0.48	0.52	0.55	0.58	0.60	0.62	0.69
87.5	0.78	1.16	1.27	1.34	1.42	1.47	1.50	1.69
90.0	1.23	1.84	2.01	2.11	2.24	2.32	2.37	2.67
92.5	1.66	2.48	2.71	2.85	3.02	3.13	3.20	3.60
95.0	2.06	3.08	3.37	3.54	3.75	3.89	3.98	4.47
97.5	2.44	3.65	3.99	4.19	4.45	4.60	4.71	5.29
100.0	2.80	4.18	4.56	4.78	5.05	5.21	5.31	5.82
102.5	2.32	3.47	3.79	3.99	4.23	4.38	4.48	5.04
105.0	1.86	2.79	3.04	3.20	3.40	3.52	3.60	4.05
107.5	1.43	2.13	2.33	2.45	2.60	2.69	2.75	3.10
110.0	1.01	1.50	1.64	1.73	1.83	1.90	1.94	2.19
112.5	0.61	0.90	0.99	1.04	1.10	1.14	1.17	1.31
114.9	0.24	0.35	0.39	0.41	0.43	0.45	0.46	0.51

Message

- Higher confidence in batch measurement
  - Allows higher toleration of variability
  - Allows higher toleration of being away from the target

SAS Acceptance Limit Table Dissolution

ACCEPTANCE LIMITS FOR DISSOLUTION (N = 6, Q = 80.0)
SAMPLING PLAN 1
(MEETING LIMITS GUARANTEES WITH 99.0 % ASSURANCE,
THAT AT LEAST 99.0% OF ALL FUTURE SAMPLES TESTED
FOR DISSOLUTION WILL PASS THE USP TEST)
TABLE ENTRY IS UPPER LIMIT ON CV OF 6 DISSOLUTION ASSAYS

MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)
80.2	0.05	84.2	0.94	88.2	1.75	92.2	2.44	96.2
80.4	0.09	84.4	0.98	88.4	1.79	92.4	2.46	96.4
80.6	0.14	84.6	1.02	88.6	1.83	92.6	2.49	96.6
80.8	0.19	84.8	1.06	88.8	1.86	92.8	2.51	96.8
81.0	0.23	85.0	1.11	89.0	1.90	93.0	2.53	97.0
81.2	0.28	85.2	1.15	89.2	1.94	93.2	2.55	97.2
81.4	0.32	85.4	1.19	89.4	1.98	93.4	2.57	97.4
81.6	0.37	85.6	1.23	89.6	2.01	93.6	2.59	97.6
81.8	0.41	85.8	1.27	89.8	2.05	93.8	2.61	97.8
82.0	0.46	86.0	1.31	90.0	2.09	94.0	2.63	98.0
82.2	0.50	86.2	1.35	90.2	2.12	94.2	2.64	98.2
82.4	0.55	86.4	1.39	90.4	2.16	94.4	2.66	98.4
82.6	0.59	86.6	1.43	90.6	2.19	94.6	2.67	98.6
82.8	0.64	86.8	1.47	90.8	2.23	94.8	2.68	98.8
83.0	0.68	87.0	1.51	91.0	2.26	95.0	2.70	99.0
83.2	0.72	87.2	1.55	91.2	2.29	95.2	2.71	99.2
83.4	0.77	87.4	1.59	91.4	2.32	95.4	2.72	99.4
83.6	0.81	87.6	1.63	91.6	2.35	95.6	2.73	99.6
83.8	0.85	87.8	1.67	91.8	2.38	95.8	2.74	99.8
84.0	0.90	88.0	1.71	92.0	2.41	96.0	2.75	100.0

Message

- As the results get farter away from the edge of failure
  - Larger variability is tolerated

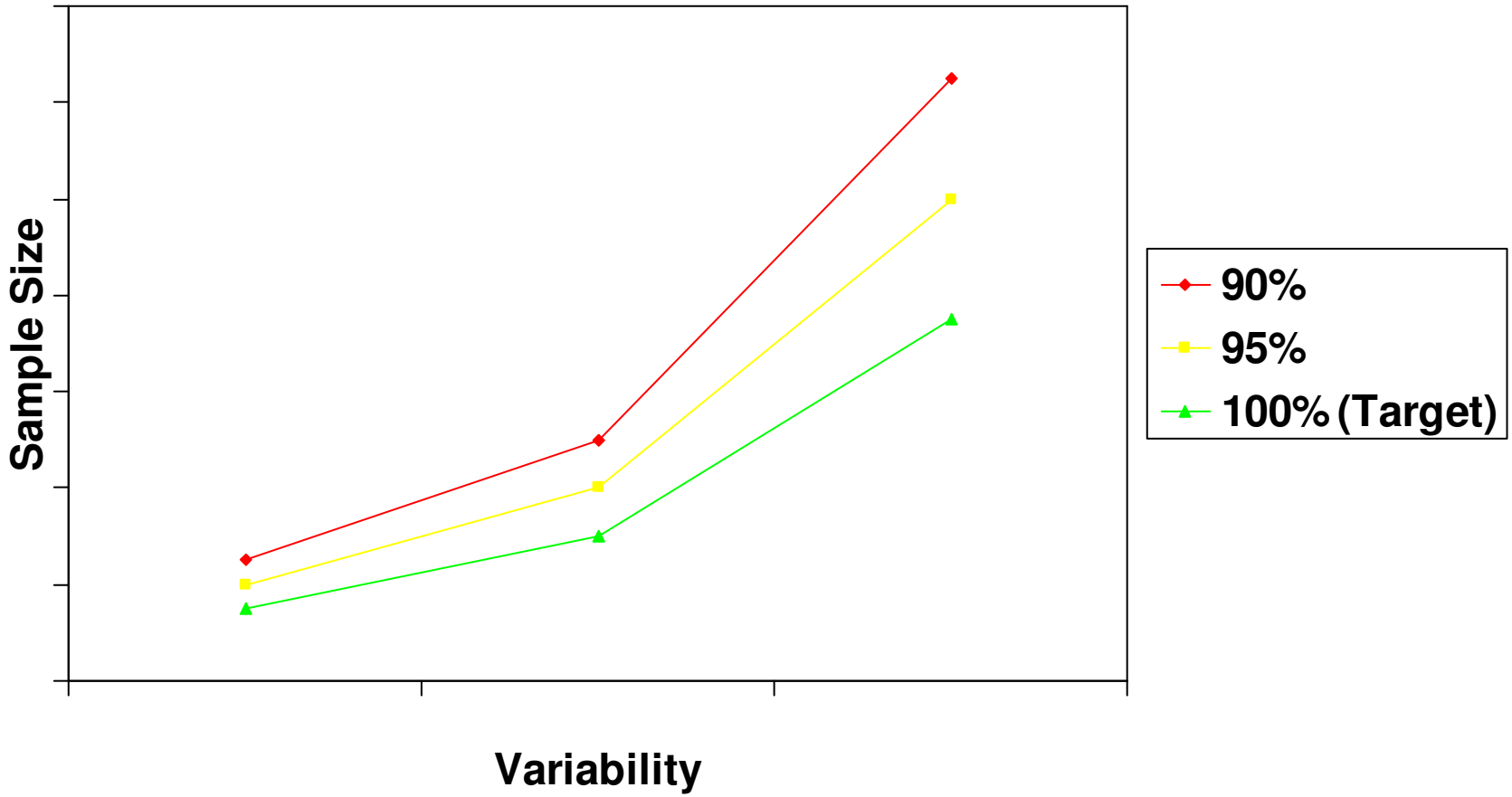
- Same is true for Uniformity of Dosage Unit Testing (UDU)

SAS Acceptance Limit Table UDU

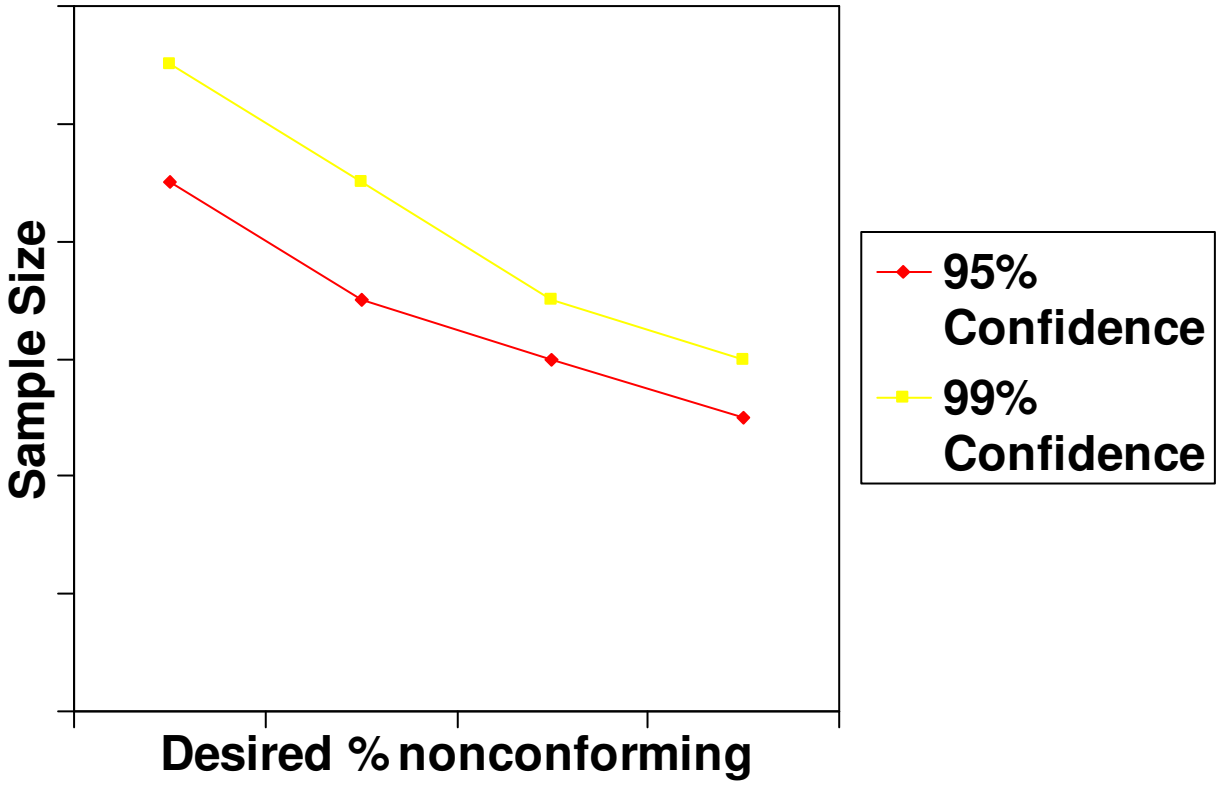
ACCEPTANCE LIMITS FOR CONTENT UNIFORMITY(N= 10, TARGET = 100.0)
SAMPLING PLAN 1
(MEETING LIMITS GUARANTEES, WITH 99.0% ASSURANCE, THAT AT LEAST
99.0% OF SAMPLES TESTED FOR CONTENT UNIFORMITY WILL PASS THE USP TEST)

MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)	MEAN (% CLAIM)	CV (%)
85.1	0.23	90.1	0.89	95.1	1.48	100.1	1.98	105.1	1.31	110.1	0.70
85.2	0.24	90.2	0.90	95.2	1.49	100.2	1.97	105.2	1.30	110.2	0.69
85.3	0.25	90.3	0.91	95.3	1.50	100.3	1.95	105.3	1.29	110.3	0.68
85.4	0.27	90.4	0.92	95.4	1.51	100.4	1.94	105.4	1.27	110.4	0.67
85.5	0.28	90.5	0.94	95.5	1.52	100.5	1.92	105.5	1.26	110.5	0.66
85.6	0.30	90.6	0.95	95.6	1.53	100.6	1.91	105.6	1.25	110.6	0.65
85.7	0.31	90.7	0.96	95.7	1.54	100.7	1.90	105.7	1.24	110.7	0.63
85.8	0.32	90.8	0.97	95.8	1.55	100.8	1.88	105.8	1.22	110.8	0.62
85.9	0.34	90.9	0.98	95.9	1.56	100.9	1.87	105.9	1.21	110.9	0.61
86.0	0.35	91.0	1.00	96.0	1.57	101.0	1.86	106.0	1.20	111.0	0.60
86.1	0.36	91.1	1.01	96.1	1.59	101.1	1.84	106.1	1.19	111.1	0.59
86.2	0.38	91.2	1.02	96.2	1.60	101.2	1.83	106.2	1.17	111.2	0.58
86.3	0.39	91.3	1.03	96.3	1.61	101.3	1.81	106.3	1.16	111.3	0.57
86.4	0.41	91.4	1.05	96.4	1.62	101.4	1.80	106.4	1.15	111.4	0.55
86.5	0.42	91.5	1.06	96.5	1.63	101.5	1.79	106.5	1.14	111.5	0.54
86.6	0.43	91.6	1.07	96.6	1.64	101.6	1.77	106.6	1.12	111.6	0.53
86.7	0.45	91.7	1.08	96.7	1.65	101.7	1.76	106.7	1.11	111.7	0.52
86.8	0.46	91.8	1.09	96.8	1.66	101.8	1.75	106.8	1.10	111.8	0.51
86.9	0.47	91.9	1.11	96.9	1.67	101.9	1.73	106.9	1.09	111.9	0.50
87.0	0.49	92.0	1.12	97.0	1.68	102.0	1.72	107.0	1.07	112.0	0.49
87.1	0.50	92.1	1.13	97.1	1.69	102.1	1.71	107.1	1.06	112.1	0.47
87.2	0.51	92.2	1.14	97.2	1.70	102.2	1.69	107.2	1.05	112.2	0.46
87.3	0.53	92.3	1.15	97.3	1.72	102.3	1.68	107.3	1.04	112.3	0.45
87.4	0.54	92.4	1.17	97.4	1.73	102.4	1.67	107.4	1.03	112.4	0.44
87.5	0.55	92.5	1.18	97.5	1.74	102.5	1.65	107.5	1.01	112.5	0.43
87.6	0.57	92.6	1.19	97.6	1.75	102.6	1.64	107.6	1.00	112.6	0.42
87.7	0.58	92.7	1.20	97.7	1.76	102.7	1.63	107.7	0.99	112.7	0.41
87.8	0.59	92.8	1.21	97.8	1.77	102.8	1.61	107.8	0.98	112.8	0.40
87.9	0.61	92.9	1.22	97.9	1.78	102.9	1.60	107.9	0.96	112.9	0.39
88.0	0.62	93.0	1.24	98.0	1.79	103.0	1.59	108.0	0.95	113.0	0.37
88.1	0.63	93.1	1.25	98.1	1.80	103.1	1.57	108.1	0.94	113.1	0.36
88.2	0.64	93.2	1.26	98.2	1.81	103.2	1.56	108.2	0.93	113.2	0.35
88.3	0.66	93.3	1.27	98.3	1.82	103.3	1.55	108.3	0.92	113.3	0.34
88.4	0.67	93.4	1.28	98.4	1.83	103.4	1.53	108.4	0.90	113.4	0.33
88.5	0.68	93.5	1.29	98.5	1.84	103.5	1.52	108.5	0.89	113.5	0.32
88.6	0.70	93.6	1.31	98.6	1.85	103.6	1.51	108.6	0.88	113.6	0.31
88.7	0.71	93.7	1.32	98.7	1.86	103.7	1.49	108.7	0.87	113.7	0.30
88.8	0.72	93.8	1.33	98.8	1.87	103.8	1.48	108.8	0.86	113.8	0.29
88.9	0.73	93.9	1.34	98.9	1.88	103.9	1.47	108.9	0.84	113.9	0.28
89.0	0.75	94.0	1.35	99.0	1.89	104.0	1.45	109.0	0.83	114.0	0.26
89.1	0.76	94.1	1.36	99.1	1.90	104.1	1.44	109.1	0.82	114.1	0.25
89.2	0.77	94.2	1.37	99.2	1.91	104.2	1.43	109.2	0.81	114.2	0.24
89.3	0.78	94.3	1.39	99.3	1.92	104.3	1.42	109.3	0.80	114.3	0.23
89.4	0.80	94.4	1.40	99.4	1.93	104.4	1.40	109.4	0.79	114.4	0.22
89.5	0.81	94.5	1.41	99.5	1.94	104.5	1.39	109.5	0.77	114.5	0.21
89.6	0.82	94.6	1.42	99.6	1.95	104.6	1.38	109.6	0.76	114.6	0.20
89.7	0.84	94.7	1.43	99.7	1.96	104.7	1.36	109.7	0.75	114.7	0.19
89.8	0.85	94.8	1.44	99.8	1.97	104.8	1.35	109.8	0.74	114.8	0.18
89.9	0.86	94.9	1.45	99.9	1.98	104.9	1.34	109.9	0.73	114.9	0.17
90.0	0.87	95.0	1.46	100.0	1.99	105.0	1.32	110.0	0.71		

Variability / Sample Size Relationship



% Nonconforming / Sample Size Relationship



Impact

- Specifications may begin to look more like lower bound plots and less like simple ranges
  - Incorporates the realities of releasing units that have not been directly tested
  - Does not assume perfection in the measurement of batch quality

Impact

- Concept of meeting specification
  - May begin to include estimates of statistical confidence as part of CGMP
  - This will reveal advantages to operation in a measurement based situation
  - This will lead to PAT implementations

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