Content Uniformity Acceptance Testing for Large Sample Sizes

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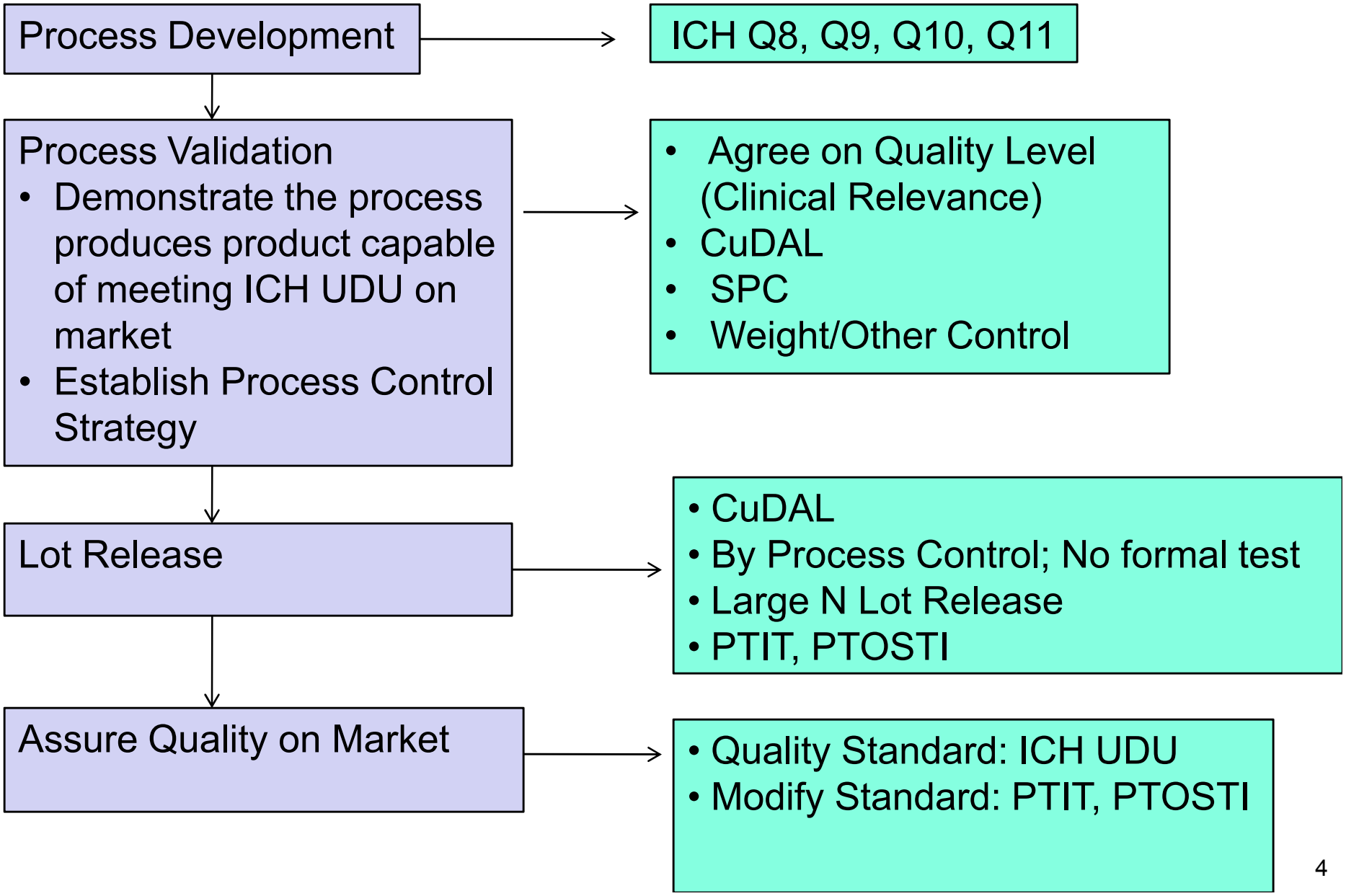
Presentation Outline

- ICH UDU and Translating Quality Requirements to Large n
- Overview of Large n Counting Test
  - 2006 to 2009 proposal
  - 2010 modified proposal
- Comments on # Tablets outside 75 – 125%
- Summary
- Questions for Audience

USP <905> Uniformity of Dosage Units

Definition: The degree of uniformity in the amount of the drug substance among dosage units.

UDU - Demonstrating & Assuring Control



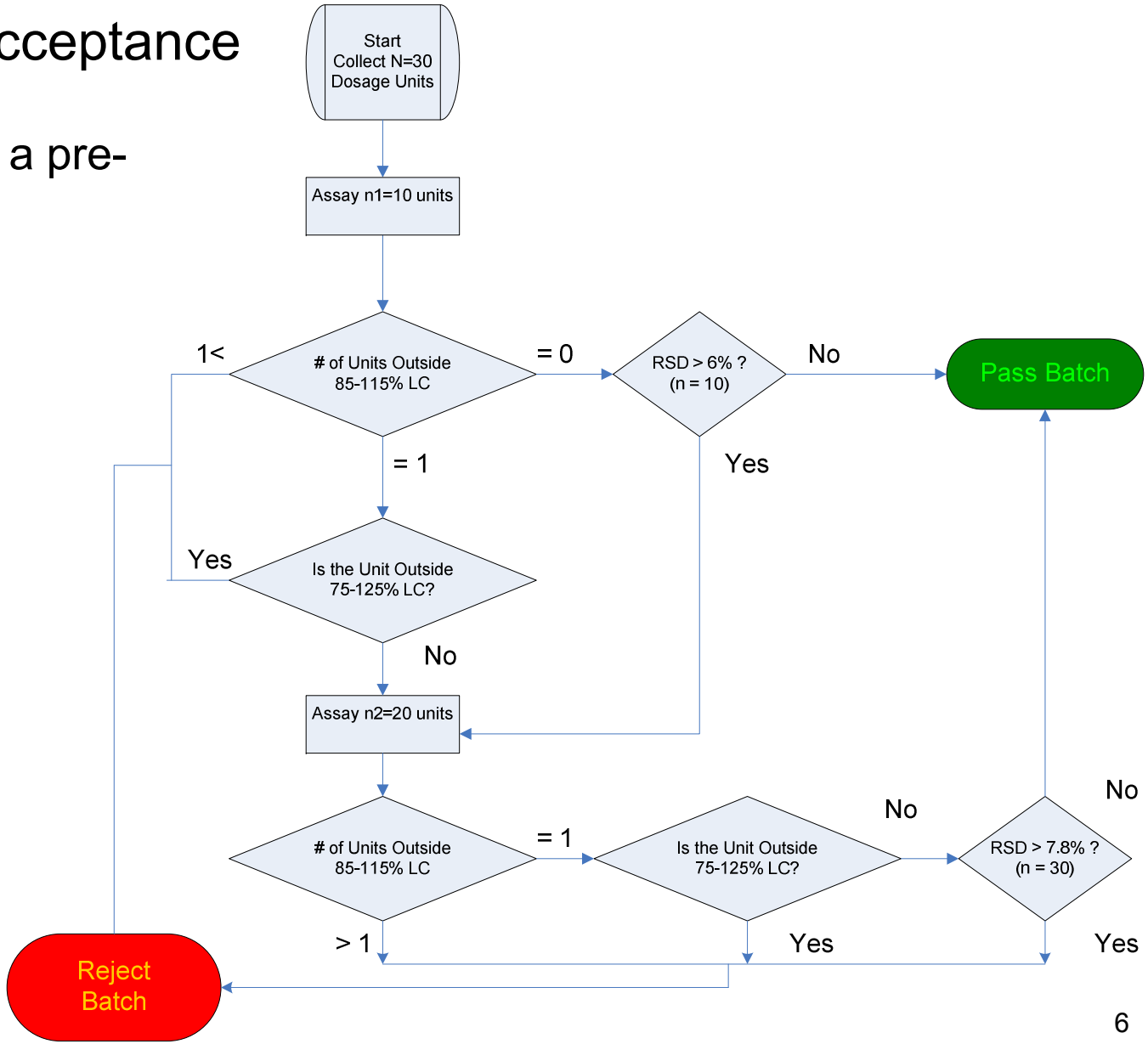
ICH UDU TEST

THE QUALITY STANDARD

Content Uniformity Test, USP <905>

<2007, two part acceptance criteria:

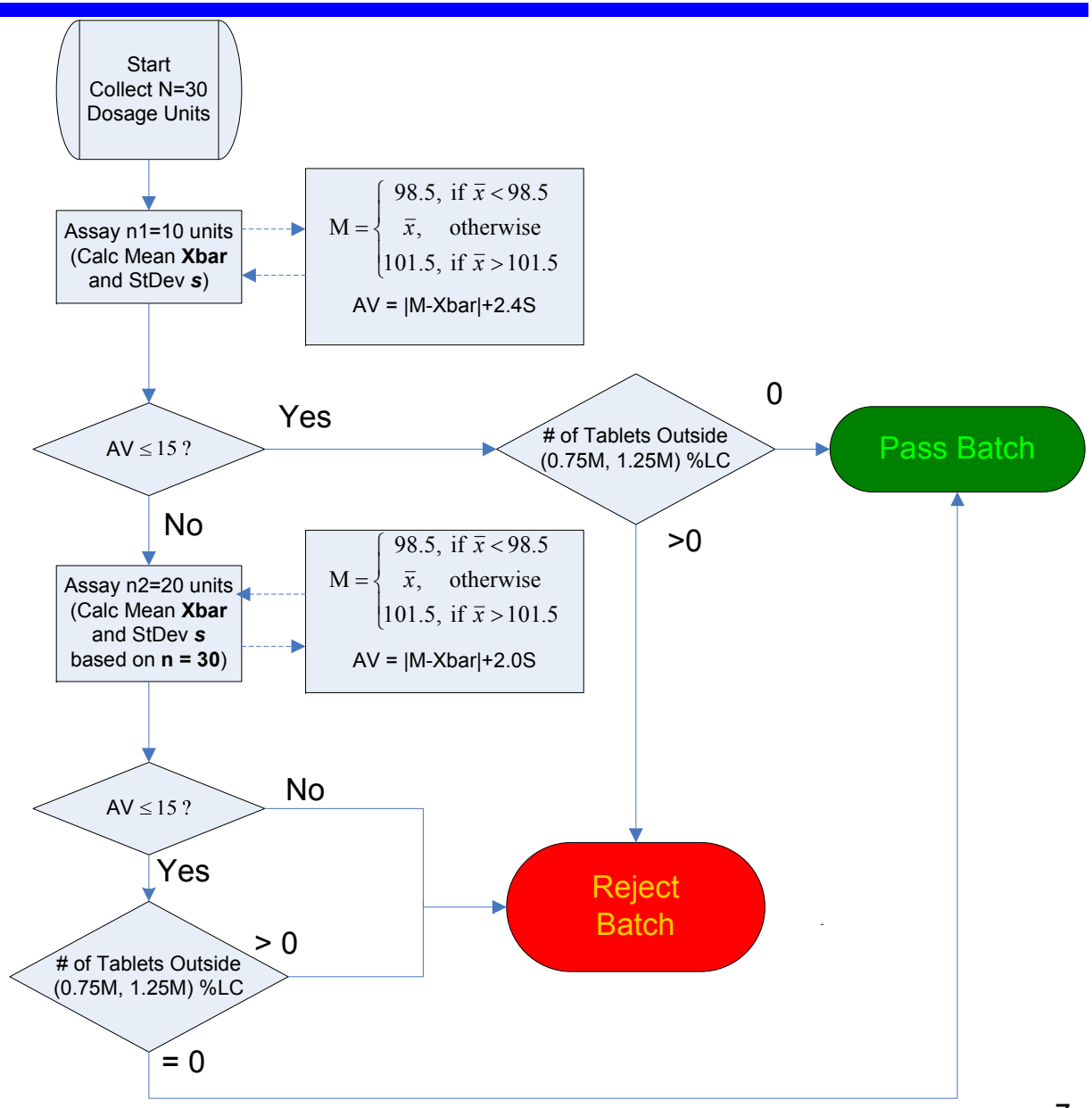
- # units outside a pre-defined range
- RSD



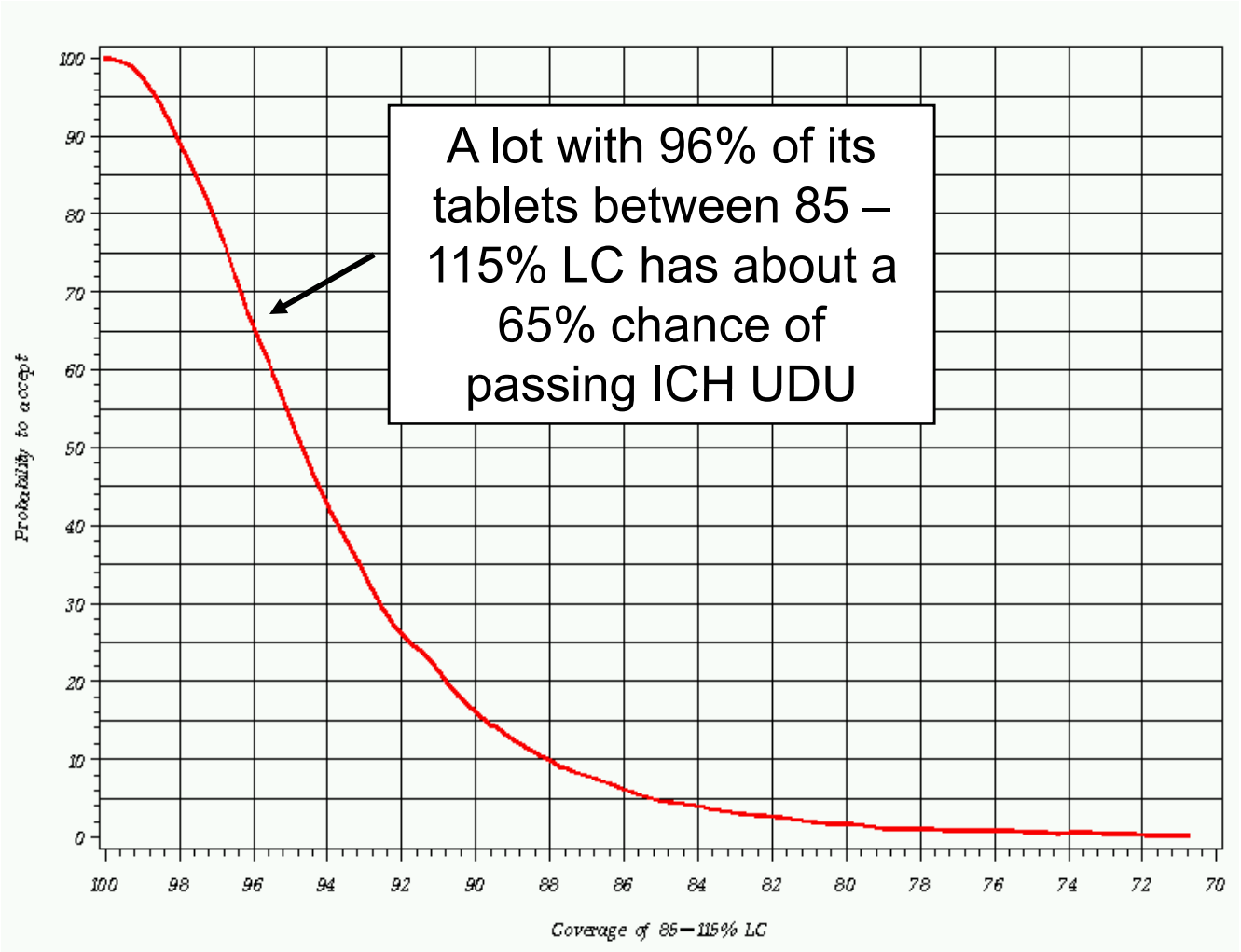
ICH UDU (2007+)

In 2007, the EP, JP, USP harmonized UDU test came into effect.

- Based on old JP test.
- Based on a two-sided tolerance interval.
- Indifference window arranged to achieve constant coverage for means within 94 – 106%
- Multiplication factors 2.4 and 2.0 equate to 84% confidence of 91% within 85 – 115%. This was not specifically calculated at the time.



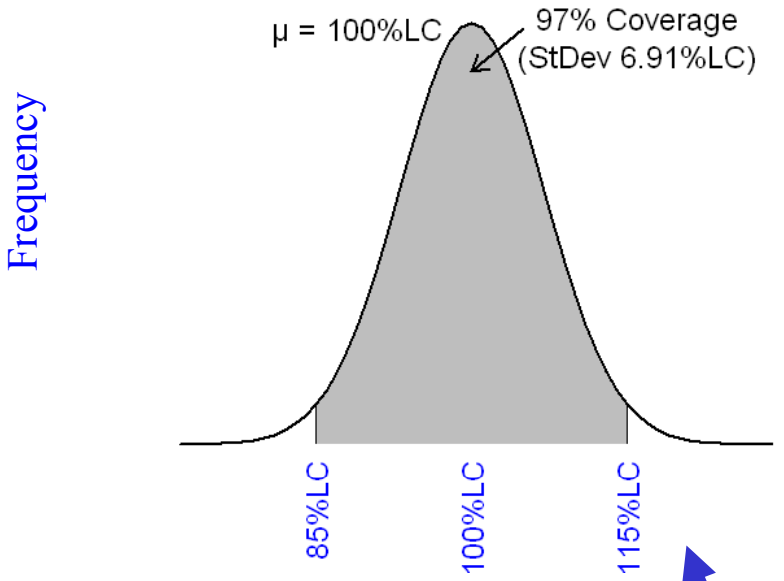
Interpretation of the OC Curve



The OC curve summarizes the test's performance providing the probability of passing the requirement given a coverage (assuming data is normally distributed.)

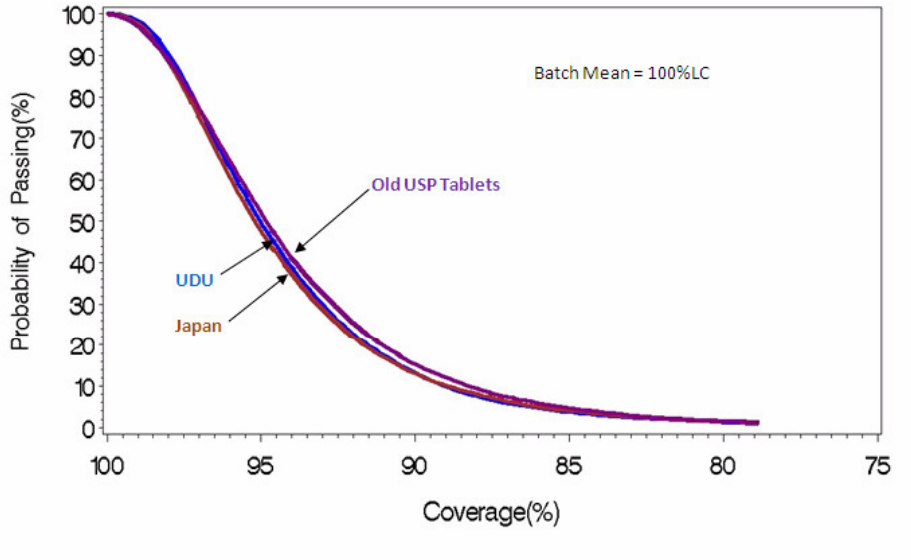
What is Coverage?

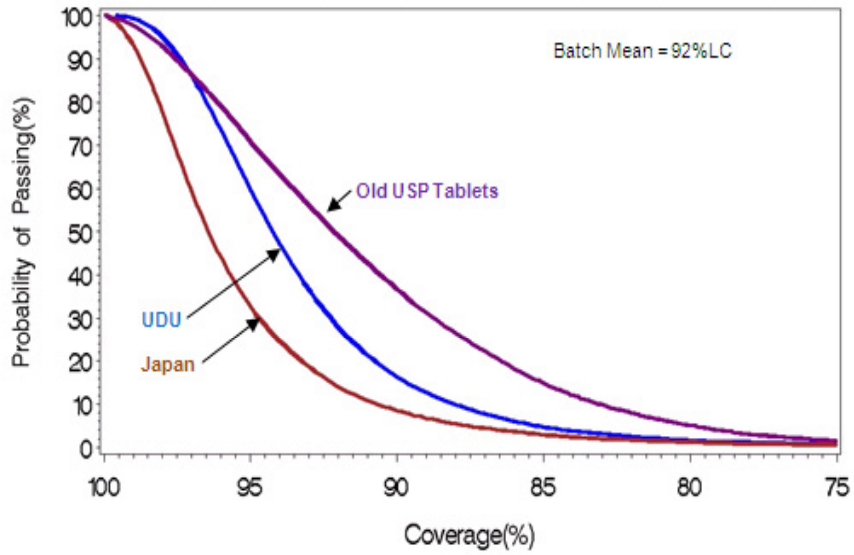
- It is a summary statistic
- It is a calculation based on both the batch mean and the standard deviation of the process (i.e., manufacturing and assay)



Mean	Std Dev	RSD	% Tablets >115	% Tablets <85%	Coverage = % of tablets within 85 - 115%	Coverage = % of tablets within 75 - 125%
100	4.0	4.0	0.01	0.01	99.98	100.0000
100	5.0	5.0	0.13	0.13	99.73	99.9999
100	6.9	6.9	1.50	1.50	97.0	99.9703
98	6.6	6.8	0.51	2.48	97.0	99.9721
96	5.8	6.1	0.05	2.94	97.0	99.9846
94	4.8	5.1	0.00	3.04	97.0	99.9962

Harmonized ICH UDU





LARGE N LOT RELEASE

Large N: The Issue and Considerations

2003 Issue:

- With PAT, n is no longer 10/30 ... A new test is required.
- How are the current quality requirements translated to large n?
- What is the appropriate acceptance test and acceptance criteria?

Considerations:

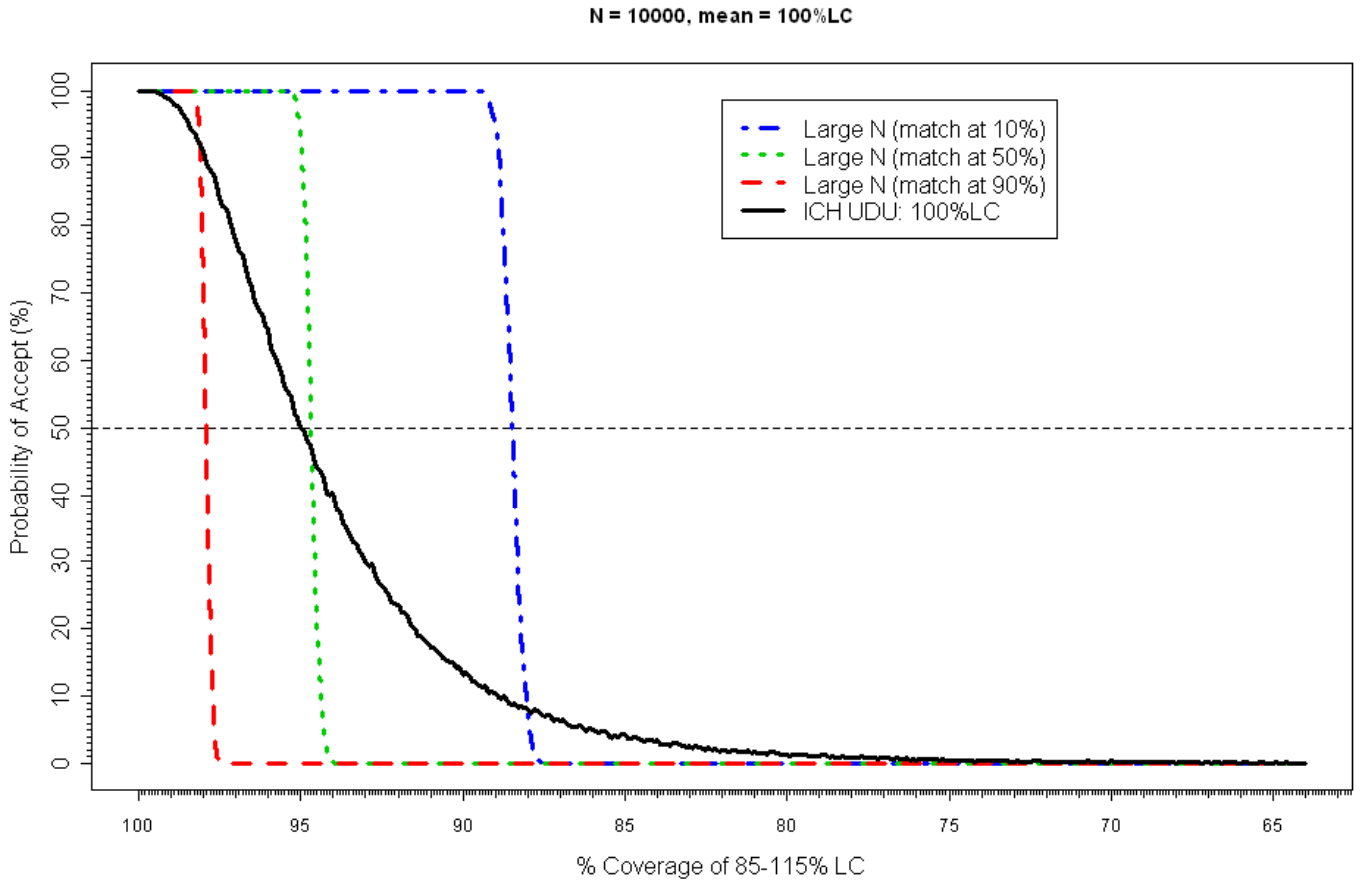
- What is the quality standard?
- Is the current quality standard acceptable?
- How to match the quality standard?
- How will the test be used?

Considerations in Developing the Large N Test

PhRMA PAT, Quality, and Statistics Team members met with the FDA (July, 2004) to Determine Test Parameters

- Quality Standard is USP 905 (now ICH UDU)
- Test should be Simple
- No Normality Assumption
- Match the ICH UDU at Probability of Acceptance = 50% (4.8% OOS at match point)

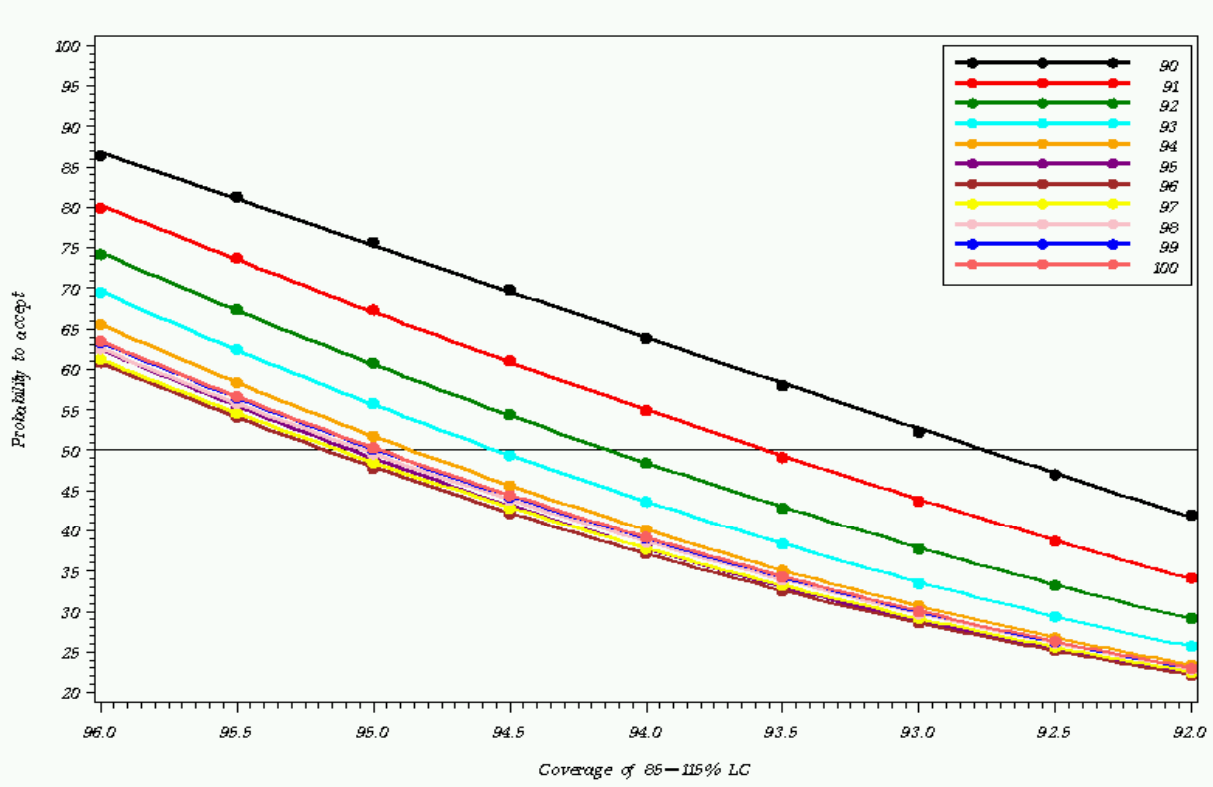
Large N Test: Where to Match ICH UDU?



Matching Quality

The coverage corresponding to a
10%, 50%, 90%
probability of accepting the lot is
88.07%, 94.68%, 98.1%.

Matching Quality: Matching which 50%?



- A maximal coverage of 95.17% (95.2%) is attained for a mean of 96.24% (96%) LC
- In large n test development, coverage of 95.2% was used
- The acceptance probability of a batch with 95% coverage of 85-115% LC is (for any mean) the same or tighter than the ICH-UDU test

Large N Test: Three Options Considered

Parametric Tolerance Interval

- Analyze n dosage units.
- Express each individual result in % of label claim
- Calculate the average and standard deviation
- Look in Table (TBD) for a k-value
- Calculate statistic and determine lot status
- Too complicated … issues with testing for normality

n	LC	k
100	100%	1.902
500	100%	1.943
100	96%	2.836
500	96%	2.873

Distribution Free Tolerance Interval

- Collect data for n dosage units; normalize to % label claim
- Order sample $x_{(1)}$, …, $x_{(n)}$
- Tolerance interval (TI) = ($x_{(L)}$, $x_{(U)}$); where L & U are determined by binomial probabilities (and depend on n)
- Accept batch if TI $\subseteq$ (85, 115)
- Cool idea ... very very complicated

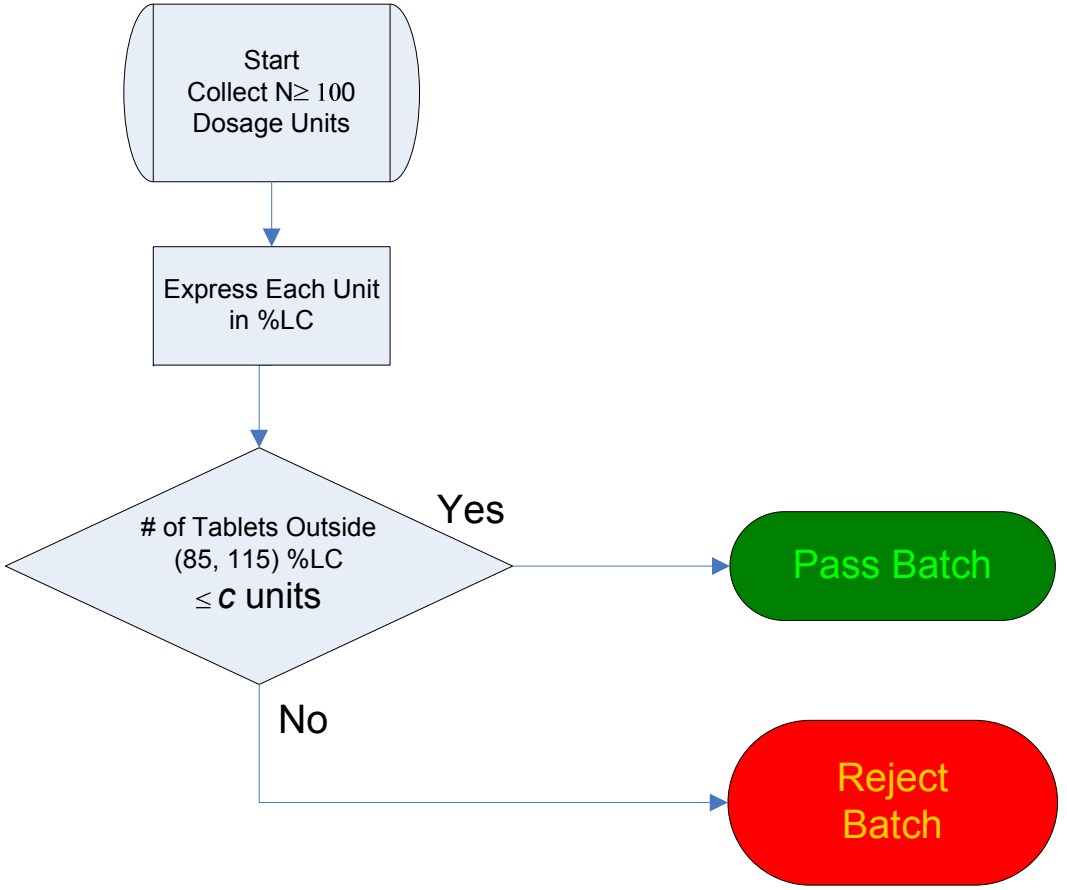
Coverage (%)	Sample size (n)	Order statistics	
		Lower	Upper
87.5	100	3	97
90.0	200	6	194
91.5	300	9	292
91.75	400	12	389
92.25	500	14	486

Nonparametric Counting Test

Large N Counting Test

- Paper Published "Development of a Content Uniformity Test Suitable for Large Sample Sizes," *Drug Information Journal* 40 (3), 337-344 (2006).
- One tiered counting test
- Test translates to finding the largest integer t, called c, such that:

$c = \max\{t ; \text{Prob}(Y \leq t \,||\, p = 0.048) \leq 0.5\}$.

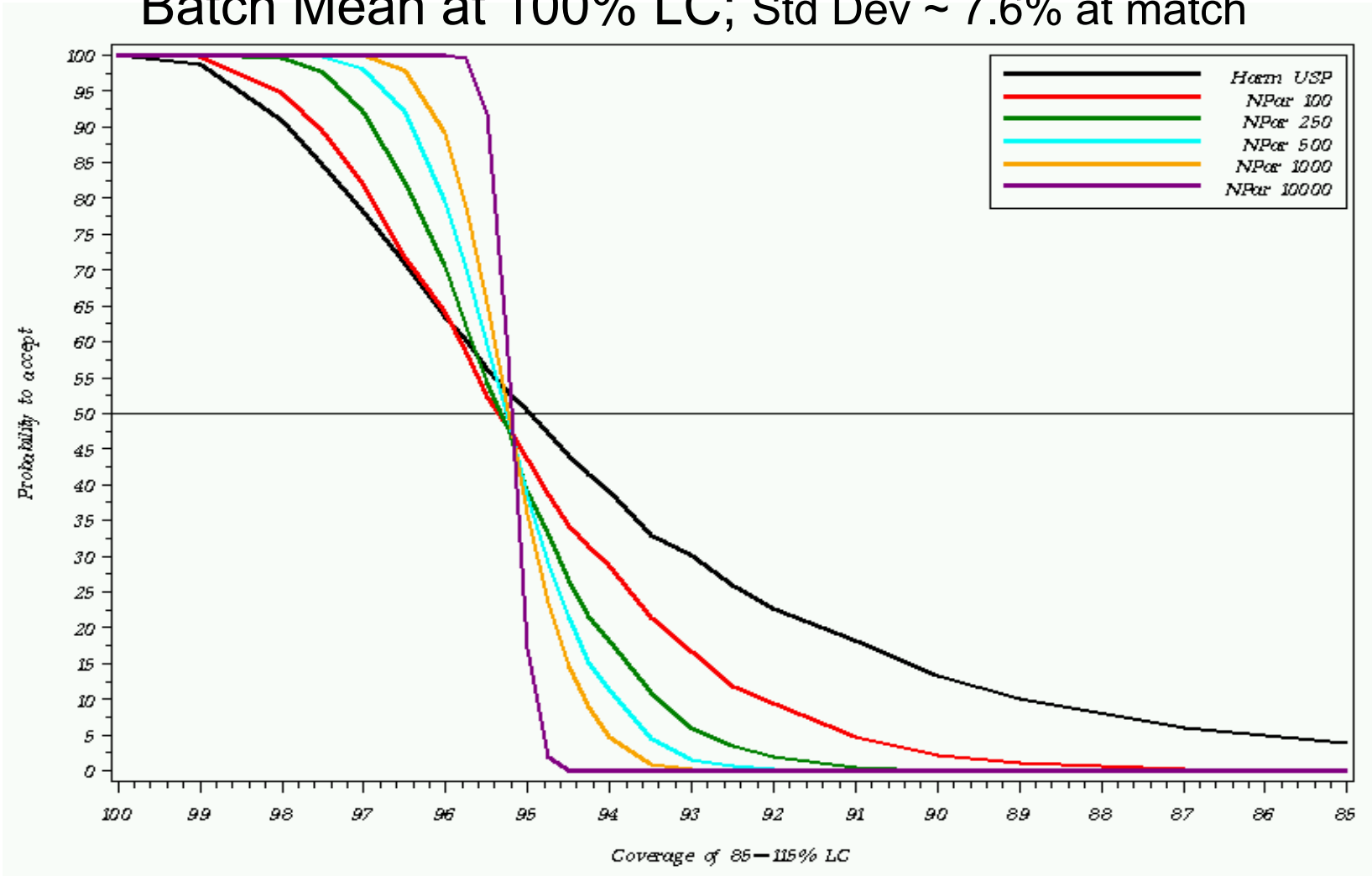


n	100	250	500	750	1000	2000	3000	4000	5000	10000
c	4	11	23	35	47	95	143	191	239	479

c = round(-1.15+0.048*n)

Large N Counting Test Performance

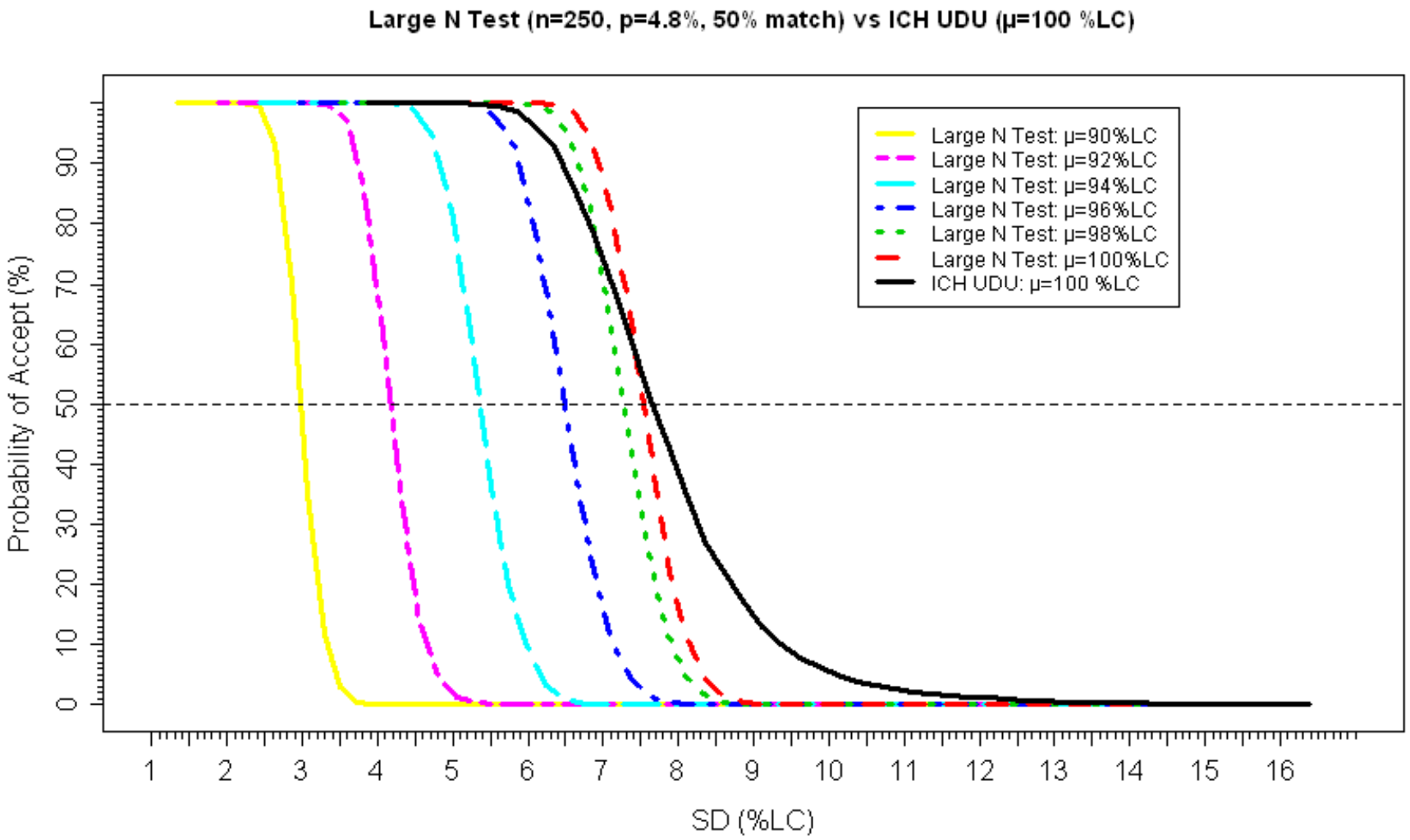
Batch Mean at 100% LC; Std Dev ~ 7.6% at match



Large N OC curves are strictly to the left of the harmonized UDU test OC curve at the 50% pass line.

Large N Counting Test Performance, n=250

Quality requirements tighten as the mean is off target.



Advantages of Large N

- Simple Test Mathematically
- Simple to Implement (no look up table required)
- No Normality Assumption Required
- Quality More discriminating than ICH UDU

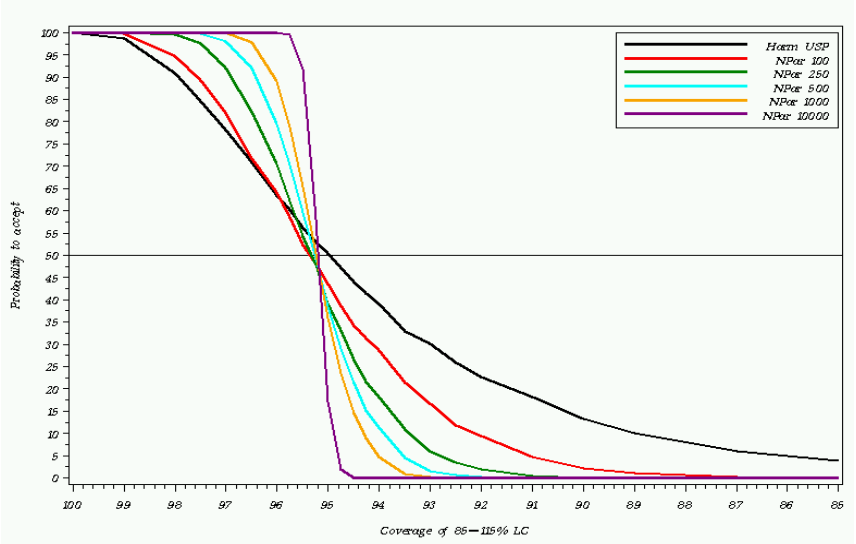
Mixed Response to Matching at 50%

Negatives

- Increased sample size creates increased probability to pass the test (many disagree as this depends on how quality is defined)

Positives

- Accepted as a step forward to gaining process understanding and developing an acceptable test



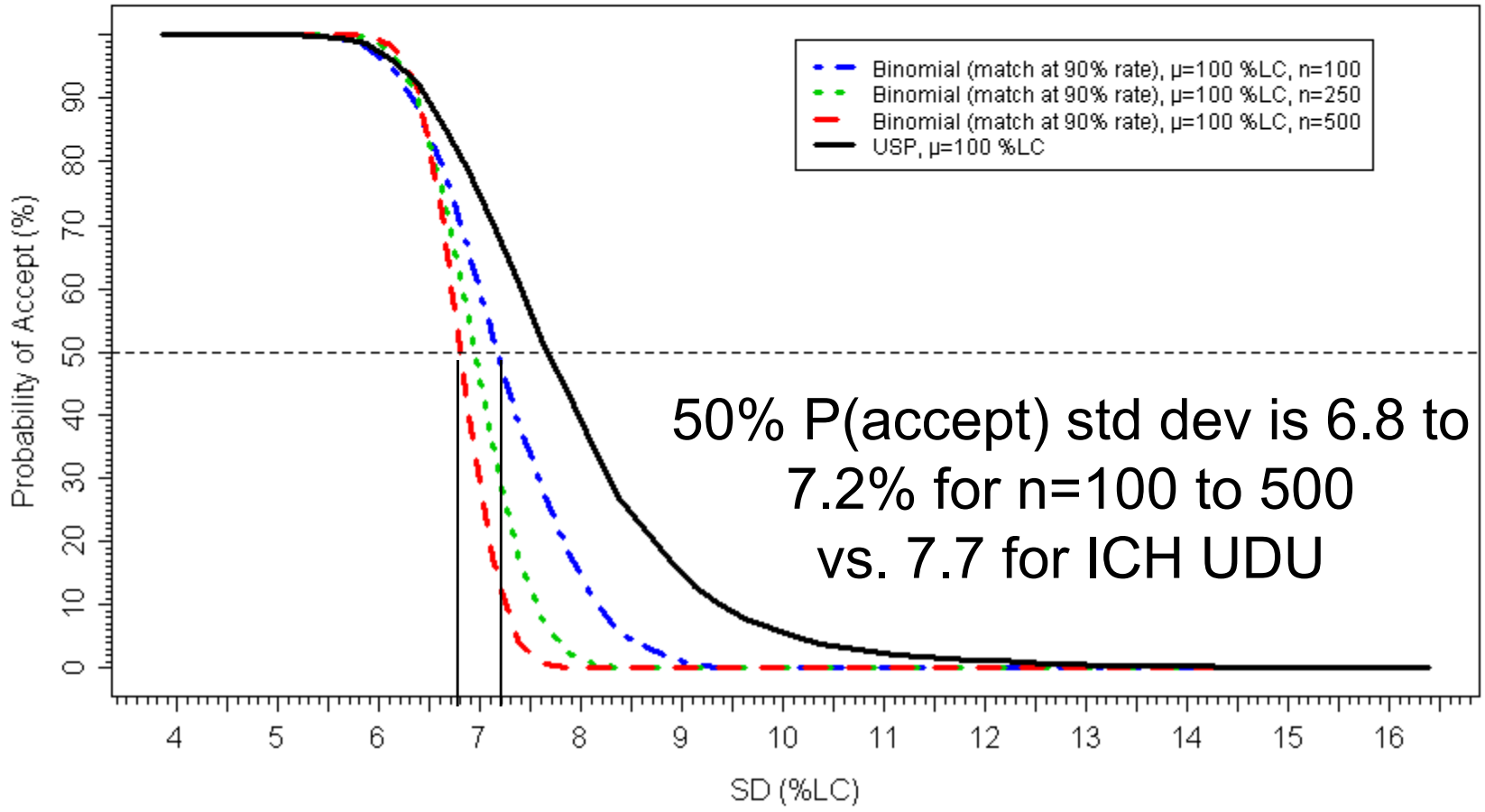
MODIFIED LARGE N

Modified Large N

- Two proposals evaluated:
  - Matching at 90%
  - Maintaining a constant 3% of units outside 85 – 115%
- Number of tablets outside 75 – 125% considered

90% matching point for mu = 100%

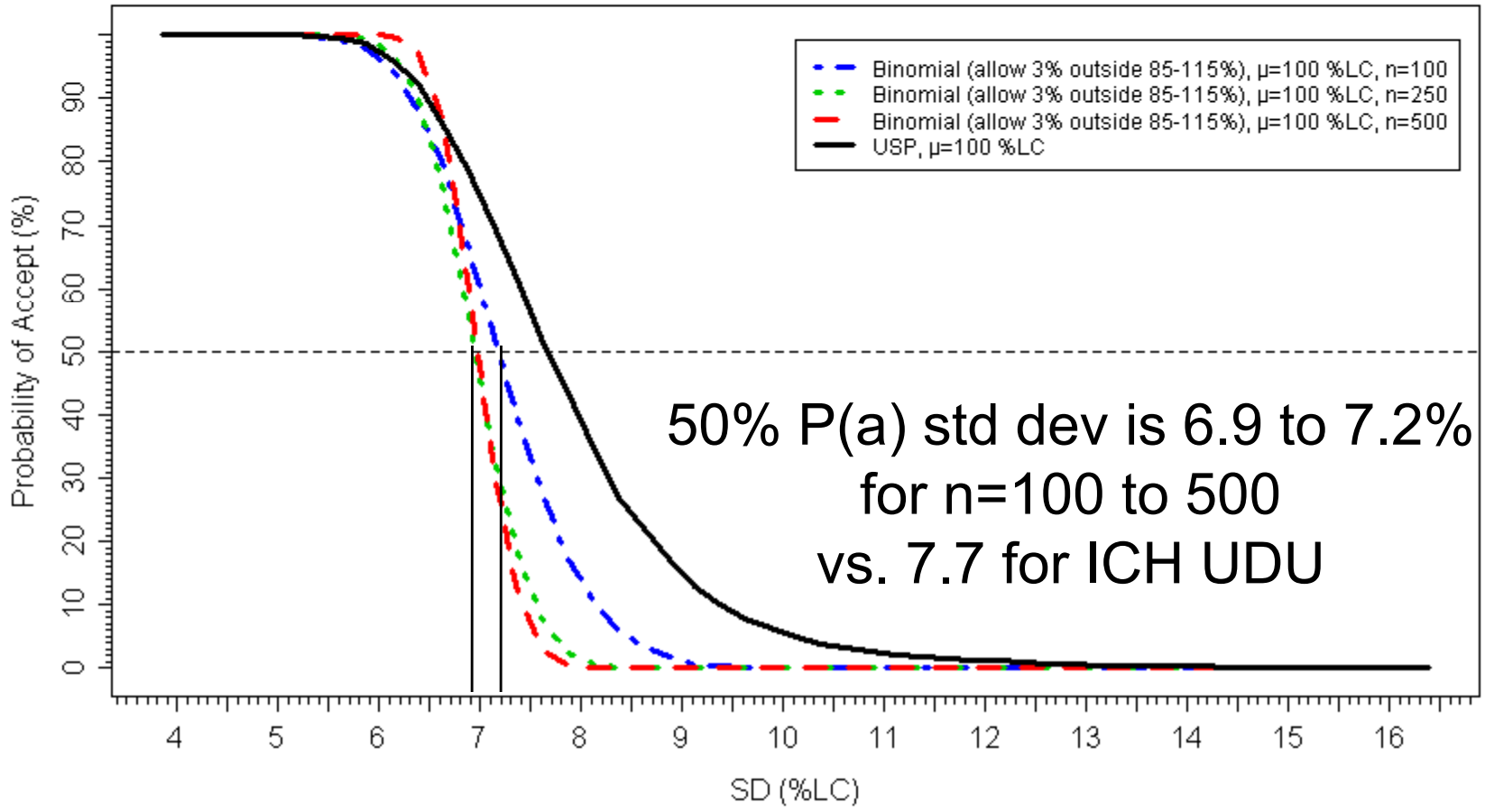
The test translates to finding the largest integer t, called c, such that:
$c = \max\{t ; \text{Prob}(Y \leq t \,||\, p = 0.02) \leq 0.9\}$.



c is 3, 7, 13 for n=100, 250, 500.

3% Outside 85 – 115% for mu = 100%

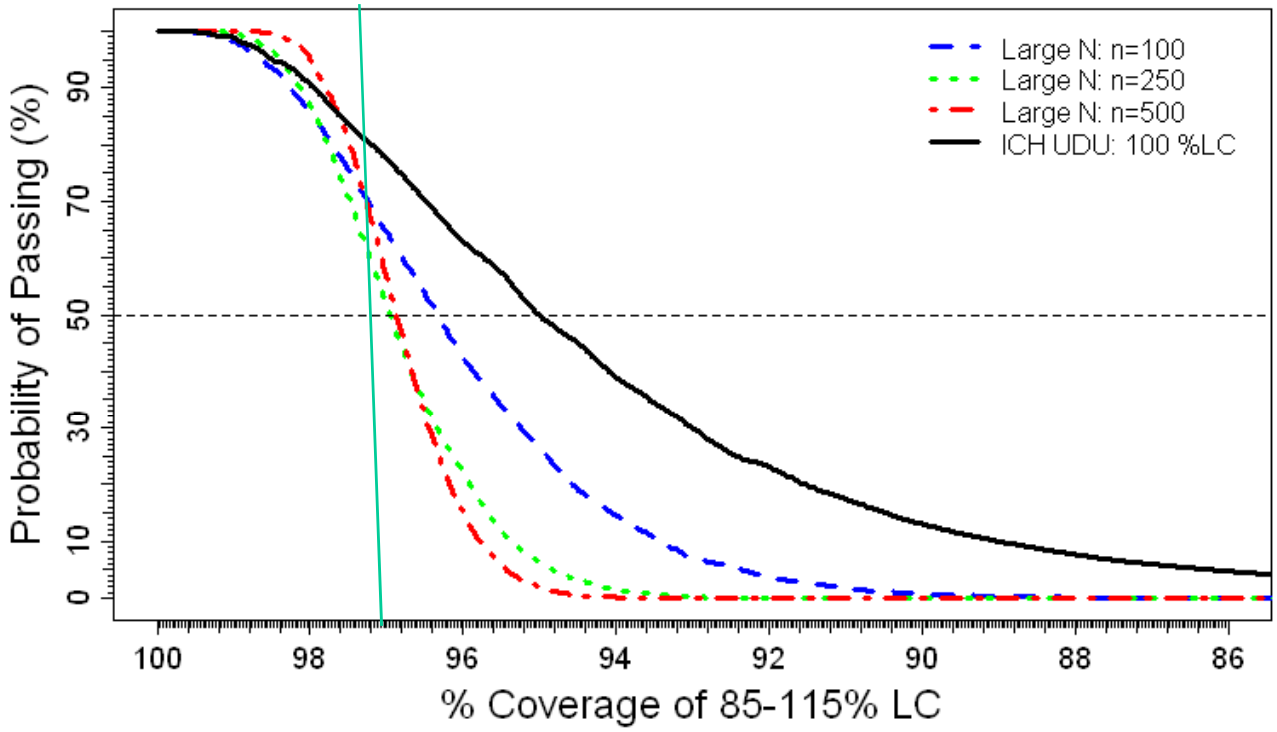
Set Quality Level (QL) = 1 – coverage (e.g. 3%)
C = Floor(p*N), where p = proportion of N outside [85, 115]
=> Same proportion used for all N.



c is 3, 7, 15 for n=100, 250, 500.

Large N Criterion: ≤ 3% Outside 85-115% LC

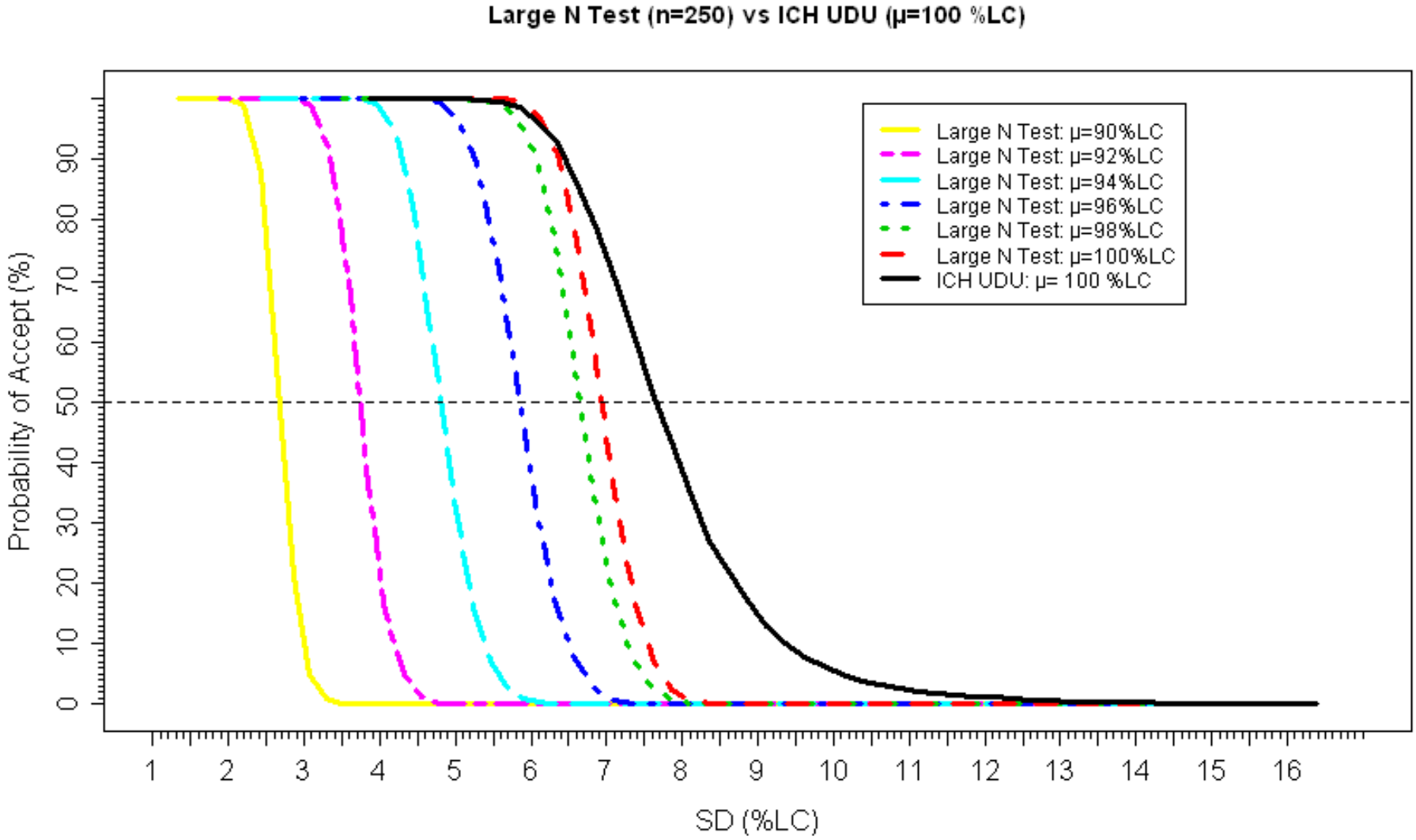
Bergum, J.; Vukovinsky, K.; "A Proposed Content Uniformity Test for Large Sample Sizes", Pharmaceutical Technology, 34 (11) 72 – 79 (2010)



Test	Sample Size	Acceptance Value
ICH UDU	10	0
ICH UDU	30	1
Large N	100	3
Large N	250	7
Large N	500	15

Modified Large N Test Performance, n=250

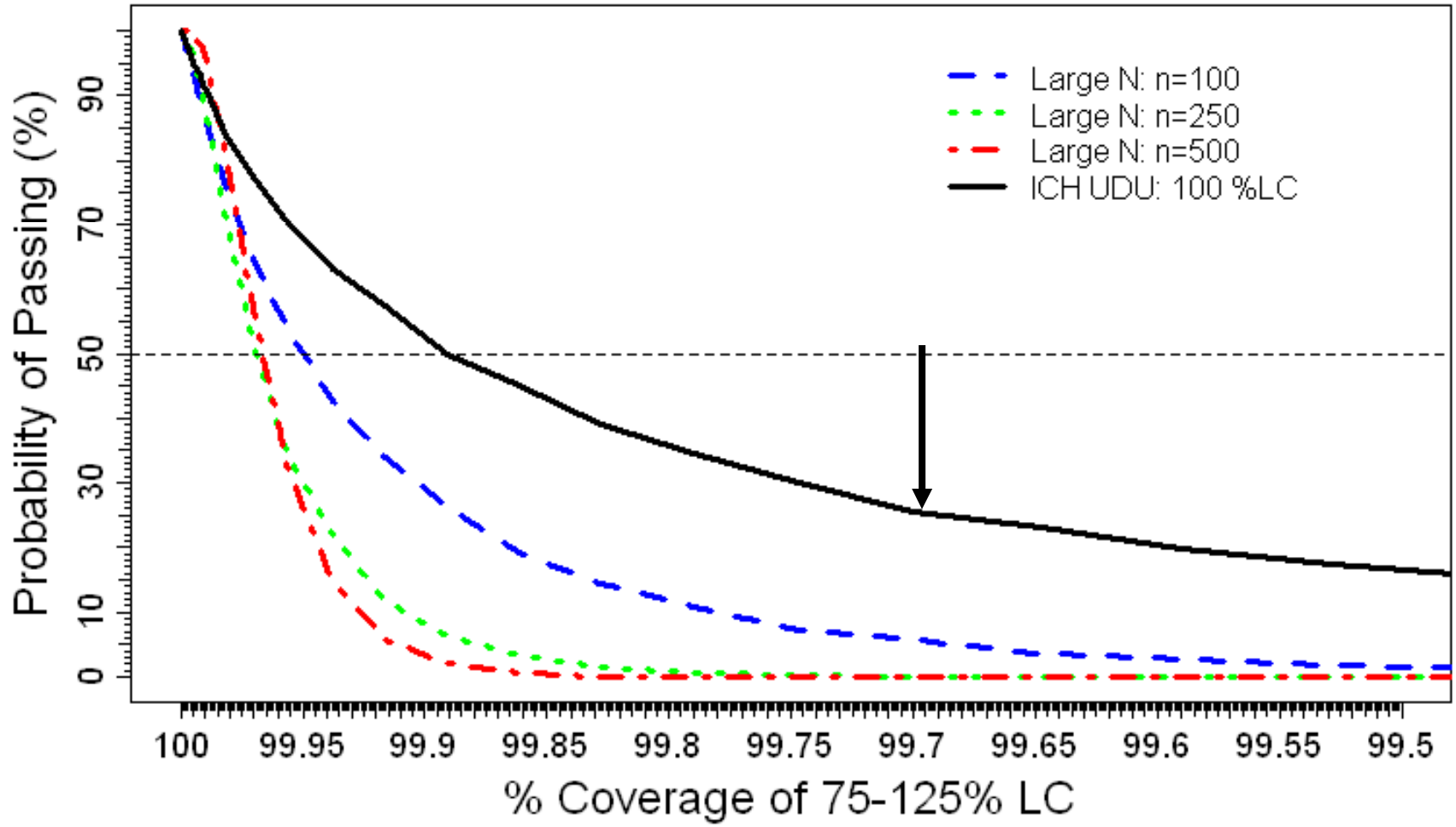
- p=3% (Match with ICH UDU is >/= 90%)



For a mean of 98 – 102%, need sd to be <5.5%

3% Large N Criterion Protects Against Results Outside 75-125% LC

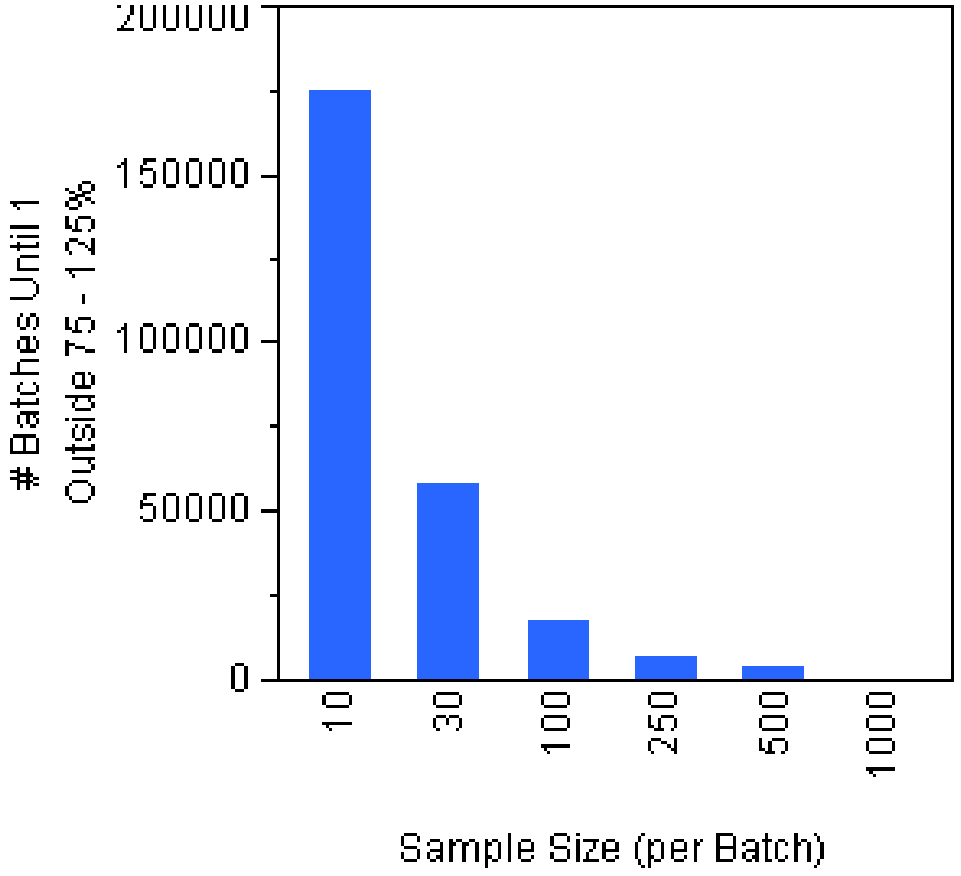
Assuming normality … the 3% counting test provides tighter control of the proportion of results outside 75-125%. A batch with 0.3% units outside 75-125% has about 25% chance to pass the ICH-UDU test, while the chance to pass the Large N 3% test is 5% for n=100 and approaches 0% for larger n.



Large N Criterion: None Specified for 75-125% LC

- Batch acceptance should depend on quality level, not sample size
  - Zero tolerance for tablets outside 75-125% LC is not acceptable

# of batches Until 1 Tablet Found Outside 75 – 125%
for a Mean of 100% LC and Std Dev of 5.0%



Summary

Advantages of Modified Counting Test

- Simple Test Mathematically
- Simple to Implement (no look up table required)
- Testing for Normality NOT Required
- Quality Level Consistent with the ICH UDU
- Increase in Sample Size Leads to a Tightened Quality Level

Large N Counting controls number of tablets outside 75 – 125% to a tighter level than ICH UDU even with no control on # outside 75 – 125%

Zero Tolerance of Tablets Outside 75 – 125% is not acceptable; at minimum will need Table with Acceptance increasing with Sample Size (1 allowed out at 200)

Acknowledgements

- Fasheng Li, Pfizer: Graphics and Discussion
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- Jeff Hofer, Eli Lilly: Large N
- Jim Pazdan, Novartis: Large N
- Joep Timmermans, Pfizer: Large N

Questions for the Audience

- Do you feel that tablet potency is normally distributed? What distribution do you expect the data will follow and why?
- Should we test for normality if using a normal based test?
- Do you feel that the release test needs to be simple?
- What is the benefit of Large N lot release?