

General Considerations for
Sampling in a PAT Environment



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Outline of Presentation

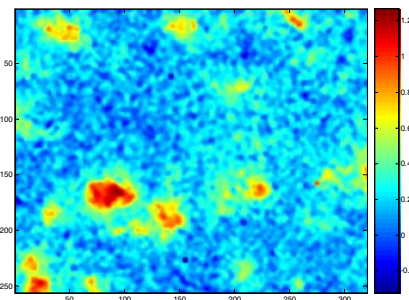
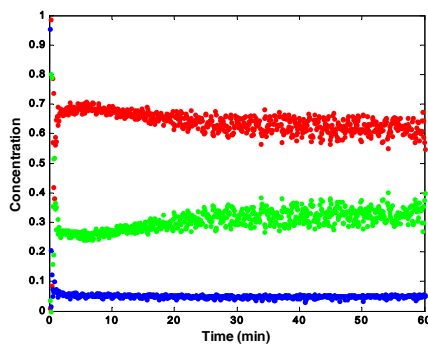
- Introductory thoughts on sampling
- Sampling Level I: Interaction with the Process
- Sampling Level II: Within-Batch Sampling
- Sampling Level III: Sampling Across Batches
- Summary

Sampling Level I: Interaction with the Process

- Critical considerations (assuming you need to add a new sensor or sampling method):
 - Where should sensors be located (samples be taken)?
 - How many sensors/locations should be interrogated?
 - What speed is required for the measurement to be “timely”?
 - Will the sensor impact the process performance; or, will the process impact sensor performance?
 - ♦ What sort of materials are required?
 - ♦ Are there critical issues w/regard to maintenance access?
- PAT measurement systems/schemes must be **designed** for the intended application
 - Critical factors affecting performance
 - Systems for continuously verifying measurement **suitability**
 - Is **redundancy** and robustness planned for in the system?

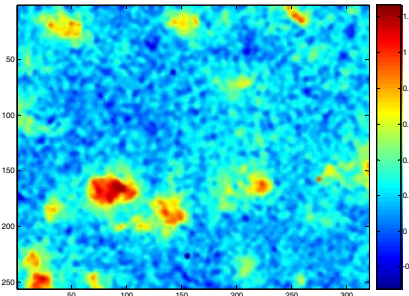
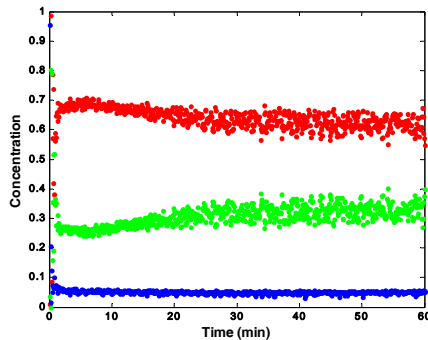
Sampling Level I: Interaction with the Process

- Situation after installing a very fancy new sensor:
 - “Why does the process never reach uniformity?”
 - “Why does the variance get worse with time?”



Sampling Level I: Interaction with the Process

- What were we forgetting to ask?
 “What is the required ‘**scale of scrutiny**,’ and
 ...what is the scale of our measurement?”



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Sampling Level I: Interaction with the Process

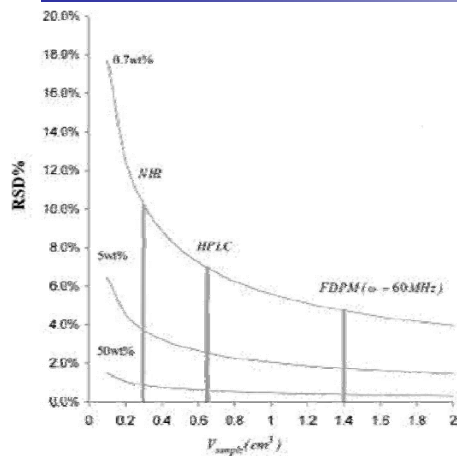
- Complete random mixture (CRM) model

$$RSD = \frac{\sigma_{CRM}}{\langle k \rangle} = \frac{1}{\sqrt{N}} \times \sqrt{\frac{1}{p} - 1}$$

- σ : true standard deviation of API concentration
- N : total particle number per sampling
- p : nominal concentration of API
- $\langle k \rangle$: expected number of API particles per sampling

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Sampling Level I: Interaction with the Process



	Sampled volume	Predicted RSD
HPLC	^a 0.65 cm ³	7%
NIRS	^b ~0.3 cm ³	~10%
FDPM	^c 1.4 cm ³	4.8%

a: measured value
b: reported value based on a single optic fiber
c: predicted value

Pan T.S., Barber D., Coffin-Beach D., Sun Z.G., Sevick-Muraca E.M. J. Pharm. Sci. 2004,93:635-645



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Sampling Level I: Interaction with the Process

- The measurement system and action criteria (e.g. endpoint criterion, release specification) must be considered as a total system-
 - Do: Adapt the specification/criterion to the requirements for material quality and the capability of the instrument.
 - Do not: Adjust the measurement system until the results match the “traditional” method.



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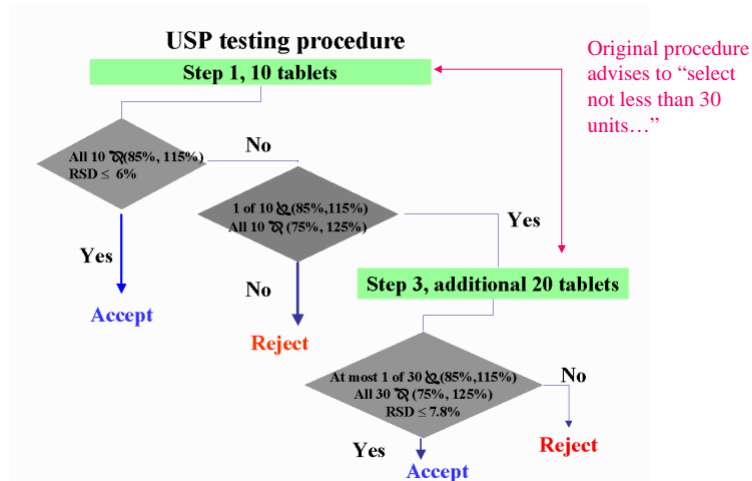
Sampling Level II: Within-Batch Sampling

- Critical considerations (now that you have a new sensor):
 - How much of the product should be sampled?
 - Suitability of “traditional” sampling methods: an analysis of USP <905>
 - ♦ PhD Research project of Phil Lunney
- See also:
 - **Validation Column: A Prevention Based Strategy for Quality Control Using PAT**, Philip Lunney and James K. Drennen, III, *NIRNews* 16/4, May/June 2005
 - **Development of a content uniformity test suitable for large sample sizes**, *PhRMA CMC Statistics Expert Team: Dennis Sandell, Myron Diener, Kim Vukovinsky, Jeff Hofer, James Pazdan, Drug Information Journal*. 40(3), August 2006

Sampling Level II: Within-Batch Sampling

- Details of USP <905> Test for Content Uniformity
 - Select 30 units from final lot
 - ♦ Random Sample not specified
 - ♦ Only 10 subjected to analysis
 - Initial Test fails if
 - ♦ One tablet lies outside of the range 85 - 115 % and/or
 - ♦ RSD > 6%
 - If initial test fails, remaining 20 are analyzed
 - ♦ Method reliability absolutely dependent on initial sample of 10

Sampling Level II: Within-Batch Sampling



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Source: FDA/CDER website

Sampling Level II: Within-Batch Sampling

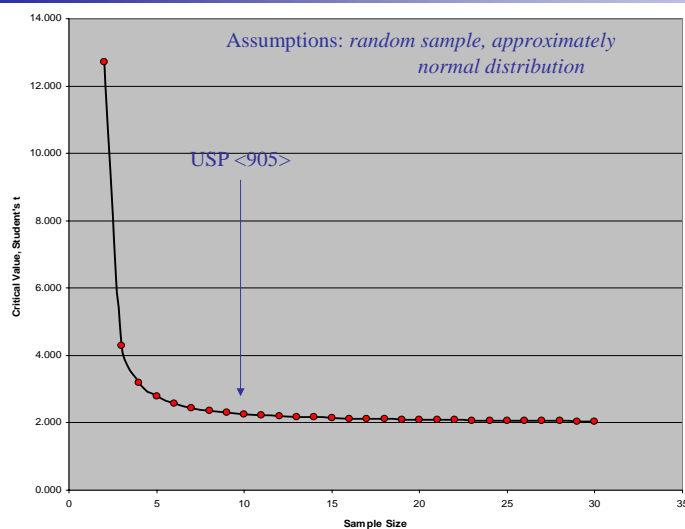
- USP does not include any reference to the origin of this procedure or make any claims with respect to its statistical validity
 - *Is it Statistically valid?*
 - ♦ *sometimes*
- The statistical validity of USP<905> depends on:
 - -the nature of the initial sample of 10
 - ♦ (and how it was collected)
 - -the statistical power of the two tests
- The two different tests have to be evaluated separately for statistical validity

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Sampling Level II: Within-Batch Sampling

- For the test to be valid, the sample must be random
 - *This has not necessarily been specified*
- *Mixed statistical basis*
 - attribute testing (yes/no) and statistical moments (RSD)
- “Power of the test” depends on the initial sample of 10
 - Sample size of 10 not likely to produce a reliable estimate of the population variance
 - ♦ *RSD portion could be entirely misleading*
 - ♦ *What is the robustness of mean and standard deviation based on 10?*
- On a “Non-Continuous Distribution” basis, the initial sample could be compared to a classical discrete probability model

Precision for Estimating the Population Mean with 95% Confidence



Sample Size Requirements for Estimating the Population Standard Deviation

To be 95% confident that “s” is within... *...of the true value of σ , the sample size “n” should be at least*

1%	19,205
5%	767
10%	192
20%	47
30%	21
40%	12
50%	8

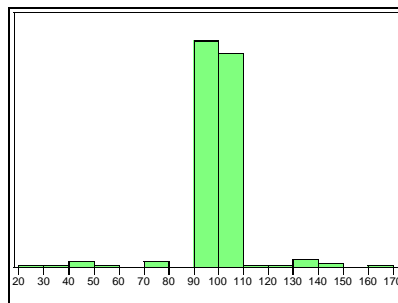
Conclusions About USP <905>, Continuous Test

- ✓ The initial sample size of 10 units is sufficient for providing a point estimate of the population mean, **assuming** that
 - The sample is taken at random
 - The underlying distribution is approximately normal
- The **initial sample size is too small** to provide a reasonable estimate of the population standard deviation
 - The inference from this portion of the test would depend on the “luck of the draw” and would likely be unreliable and possibly misleading

A proposed Model for the Attribute Test of USP<905> The Binomial Experiment

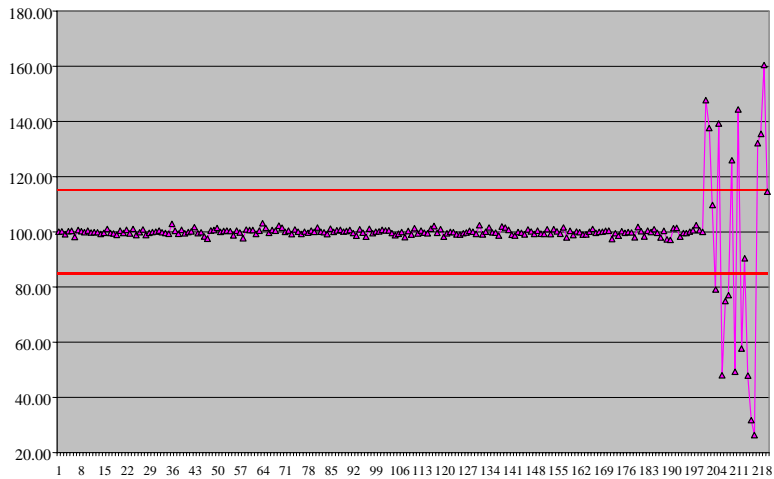
- The experiment consists of “n” identical trials
 - 10 finished units subjected to analysis
- The outcome of each trial can be classified as a “pass” or “failure”
 - *Pass within 85-115 %*
 - *Fail outside of this window*
- Probability of a Pass or Fail is constant from trial to trial
 - assumed to be equal to the unknown proportion of defects in the finished lot
 - *affected by the selection of 30?*
- The trials are independent
 - outcome of one does not influence the others

Characteristics of the Faulty Production Run



Quantiles			Moments	
100.0%	maximum	160.44	Mean	99.637409
99.5%		159.11	Std Dev	12.795879
97.5%		136.49	Std Err Mean	0.862698
90.0%		101.55	upper 95% Mean	101.33766
75.0%	quartile	100.62	lower 95% Mean	97.937156
50.0%	median	99.98	N	220
25.0%	quartile	99.31	Sum Wgt	220
10.0%		98.20	Sum	21920.23
2.5%		53.70	Variance	163.73451
0.5%		26.87	Skewness	-1.26616
0.0%	minimum	26.30	Kurtosis	15.452267
			CV	12.842444
			N Missing	0

Synthetic Test Lot of n=220 (~10% Defects)



Typical Random Sample Results Initial Sample of 10

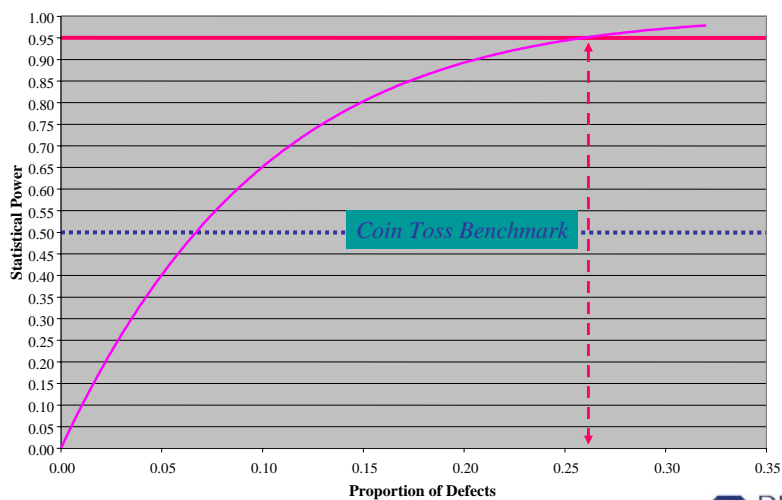
Sample	Min	Max	RSD	Result
1	99.7	102.1	0.67	Pass
2	98.9	114.6	4.61	Pass (!)
3	98.3	147.7	14.46	Fail
4	98.1	102.2	1.25	Pass
5	98.8	126.0	8.43	Fail

Binomial Probabilities for Sample Size of 10

Number of Defects	1% Defects present	5% Defects present	10% Defects present
0	.9044	.5987	.3487
1	.0914	.3151	.3874
2	.0042	.0746	.1937
3	.0001	.0105	.0574
4	.0000	.0010	.0112
5	.0000	.0001	.0015
6	.0000	.0000	.0001
7	.0000	.0000	.0000
8	.0000	.0000	.0000
9	.0000	.0000	.0000
10	.0000	.0000	.0000

This first row represents the probability of "passing" USP <905> for a given defect level

Power of the Binomial Test for N = 10

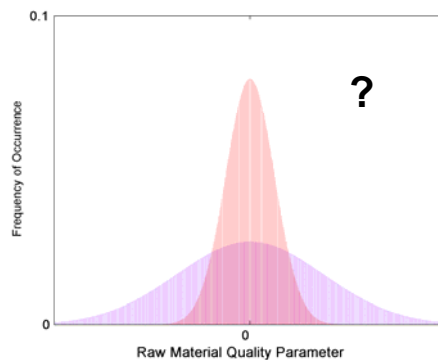


Sampling Level II: Within-Batch Sampling

- So, what does this mean?
 - How many (tablets, etc.) should be tested?
 - ♦ All of them? **NO**
 - ♦ Must sampling be in-line and automatic? **maybe**
- The question needs to change-
 - How many samples must be taken to detect a failure?
 - How **should we** sample in order to **control**?
- Current research at DCPT:
 - Determining the impact of sensor and calibration performance on sampling requirements and method suitability

Sampling Level III: Sampling Across Batches

- Has your process experienced a sufficient portion of the natural variability (after you've started watching closely)?
 - Do you know the distribution?
 - When do you know enough to control?



Sampling Level III: Sampling Across Batches

- Every measurement device has a probability of unexpected failure.
 - Redundant and/or additional sensors and samples reduce risk, but
 - Only the combination of **timely information** with **fundamental** and **experiential** understanding can be failsafe

Summary

- Sampling systems and procedures must be designed (explicitly)
 - Specifications and criteria for handling PAT data must be related to quality
- Sample for control, not for inspection
- In a PAT environment, every batch is a sample (...analysis facilitates understanding)

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