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?

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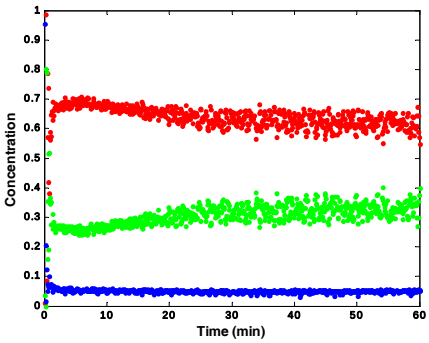
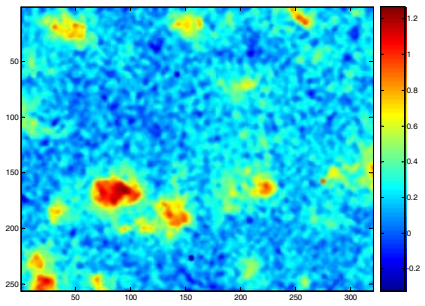
Sampling Level I: Interaction with the Process

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





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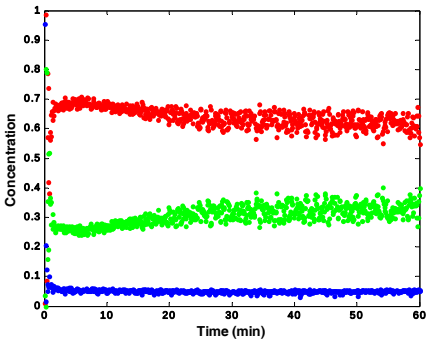
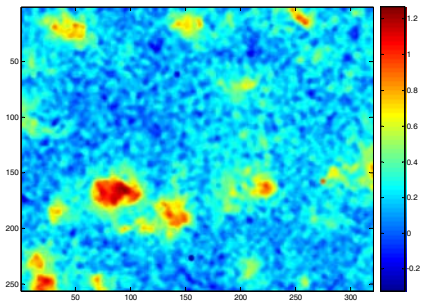
Sampling Level I: Interaction with the Process

- What were we forgetting to ask?
  "What is the required 'scale of scrutiny,' and
  …what is the scale of our measurement?"





Sampling Level I: Interaction with the Process

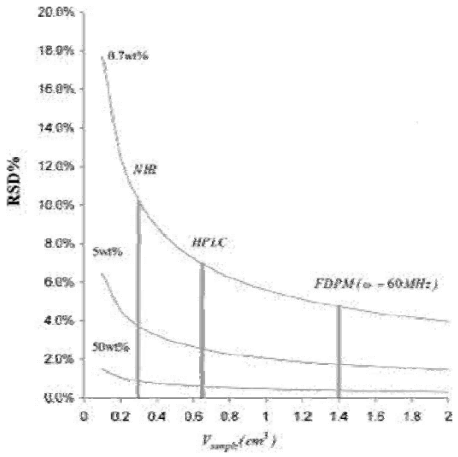
- Complete random mixture (CRM) model

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

  - σ: true standard deviation of API concentration
  - N: total particle number per sampling
  - p: nominal concentration of API
  - <k>: expected number of API particles per sampling

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

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

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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**

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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

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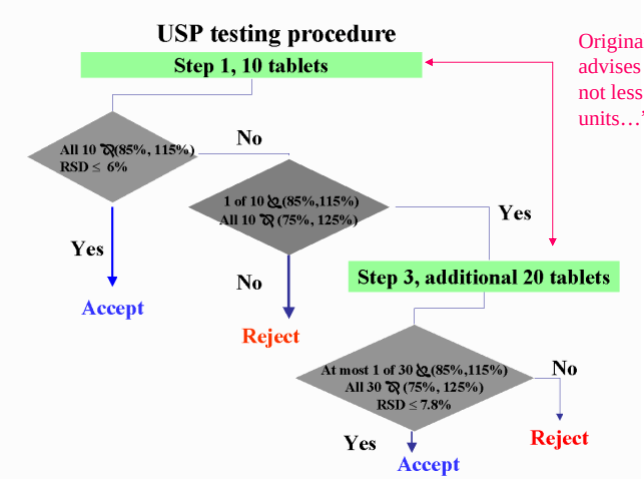
Sampling Level II: Within-Batch Sampling



Source:FDA/CDER website

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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

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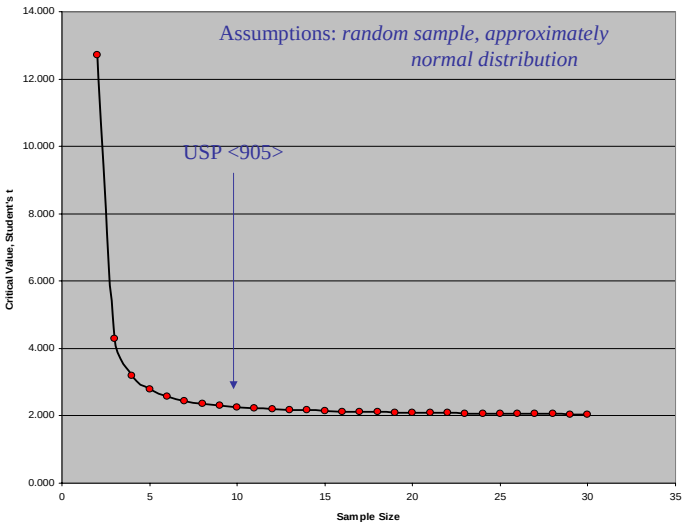
Precision for Estimating the Population Mean with 95% Confidence



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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

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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

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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

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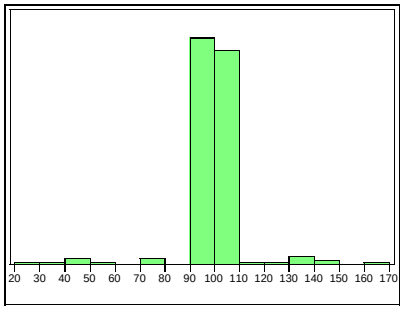
Characteristics of the Faulty Production Run



Quantiles		
100.0%	maximum	160.44
99.5%		159.11
97.5%		136.49
90.0%		101.55
75.0%	quartile	100.62
50.0%	median	99.98
25.0%	quartile	99.31
10.0%		98.20
2.5%		53.70
0.5%		26.87
0.0%	minimum	26.30

Moments	
Mean	99.637409
Std Dev	12.795879
Std Err Mean	0.862698
upper 95% Mean	101.33766
lower 95% Mean	97.937156
N	220
Sum Wgt	220
Sum	21920.23
Variance	163.73451
Skewness	-1.26616
Kurtosis	15.452267
CV	12.842444
N Missing	0

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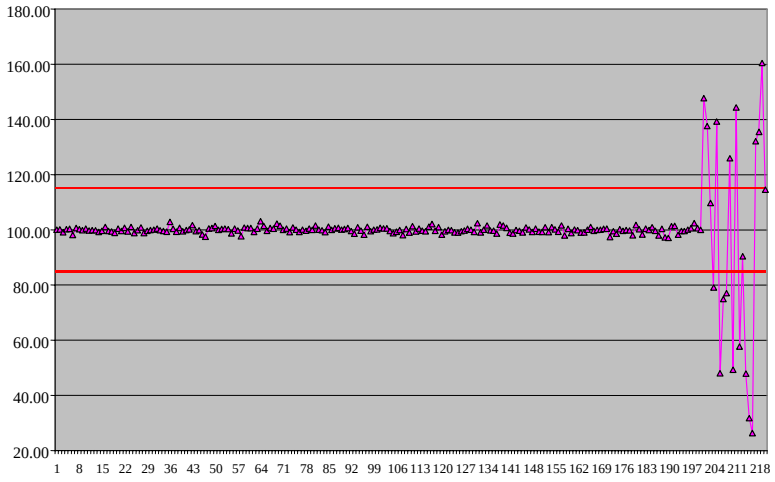
Synthetic Test Lot of n=220 (~10% Defects)



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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

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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

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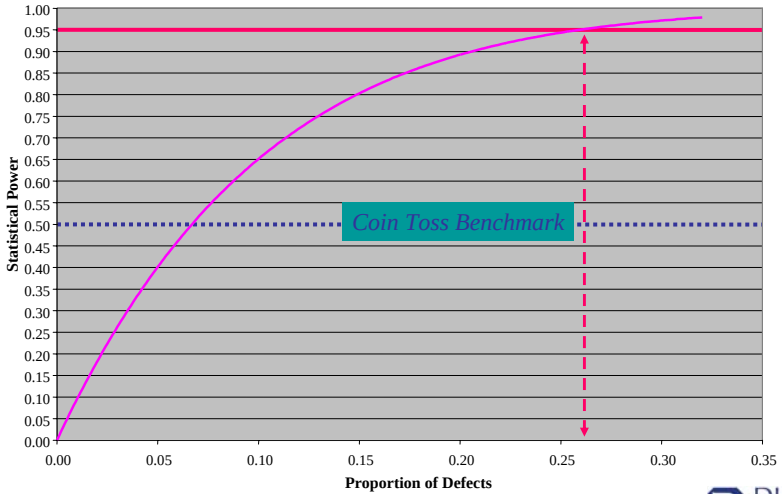
Power of the Binomial Test for N = 10



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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

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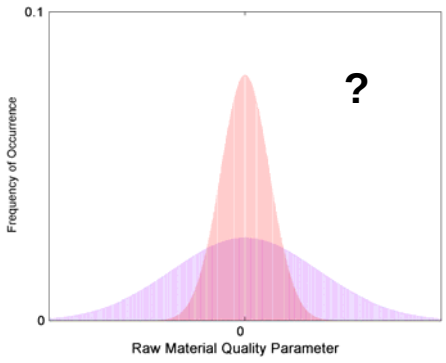
Sampling Level III: Sampling Across Batches

- 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?



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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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