# What would be the Composition a Flowing Powder if it is Analyzed Again?

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# Sources of Variation

All analytical methods are subject to random and systematic errors, whether they are PAT or off-line methods

Process Validation Guidance

- Understand the Sources of Variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes.
- Control the variation in a manner commensurate with the risk it represents to the process and product.

U.S. Department of Health and Human Services, F. D. A., Guidance for Industry Process Validation: General Principles and Practices. 2011, *Current Good Manufacturing Practices (CGMP)* (Revision 1), 1-22.

# Goals & Objectives

## "Begin with the End in Mind"

- You don't have validation unless you have a purpose (goals & objectives).
- Validation requires the need to evaluate a process, product.
- Validation requires communication with a regulatory agency to have agreed on specifications.
- If the product is already approved then you need to communicate with Quality Assurance to obtain the specifications.

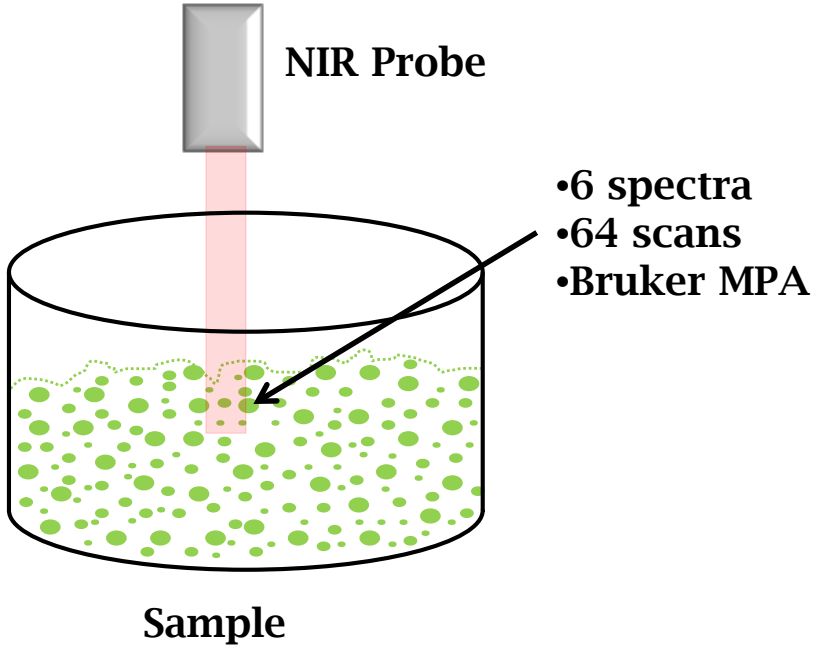
Thus the method developer or validation chemist cannot be isolated from the world, needs to communicate.

- ✓**Specifity**
- ✓**Linearity**
- ✓**Range**
- ✓**Accuracy**
- ✓**Precision**
- ✓**Repeatability**
- ✓**Intermediate Precision**
- ✓**Reproducibility**
- ✓**Detection Limit**
- ✓**Robustness**

**Validation requires communication.**

# Repeatability Study- Short term Precision

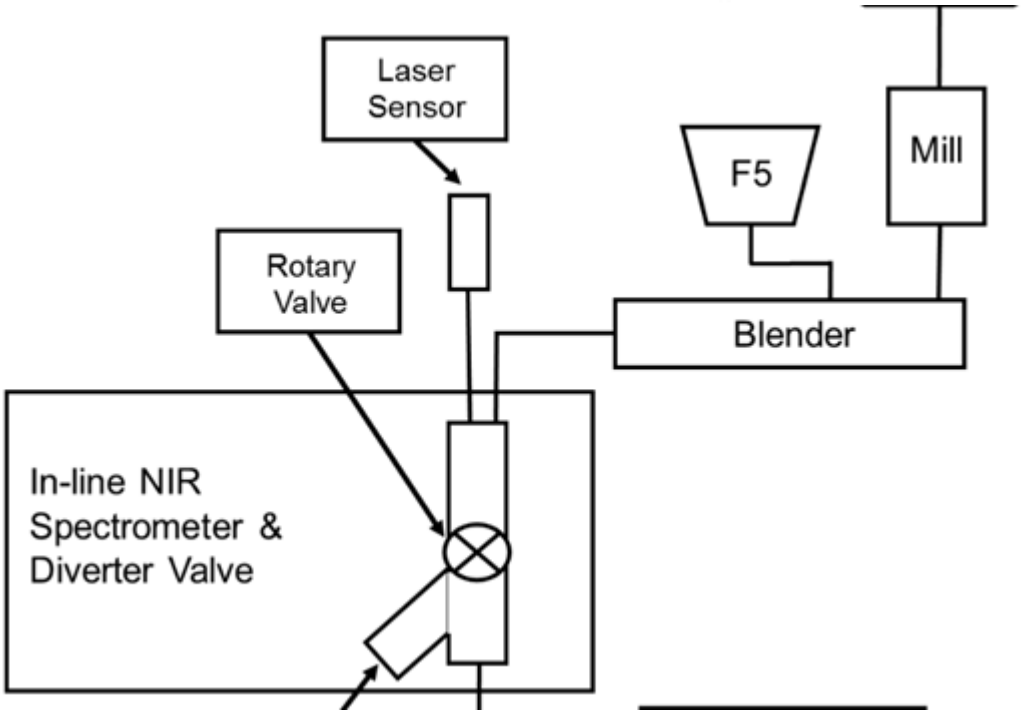
**Minimum error – as same area is analyzed the sample may be considered to be "homogeneous"**




**Repeatability study: 6 Spectra were acquired in the same spot.**

| Repeatability Study | |
|---|---|
| Exp # | Std Dev (n =6) |
| 1 | 0.1022 |
| 2 | 0.0131 |
| 3 | 0.0226 |
| 4 | 0.0316 |
| 5 | 0.0197 |
| 6 | 0.0130 |
| 7 | 0.0544 |
| 8 | 0.0138 |
| 9 | 0.0180 |
| 10 | 0.0194 |
| 11 | 0.0205 |
| 12 | 0.0409 |
| 13 | 0.0227 |
| 14 | 0.0324 |
| 15 | 0.0198 |
| 16 | 0.0168 |
| 17 | 0.0217 |
| 18 | 0.0116 |

# Description of Calibration Set



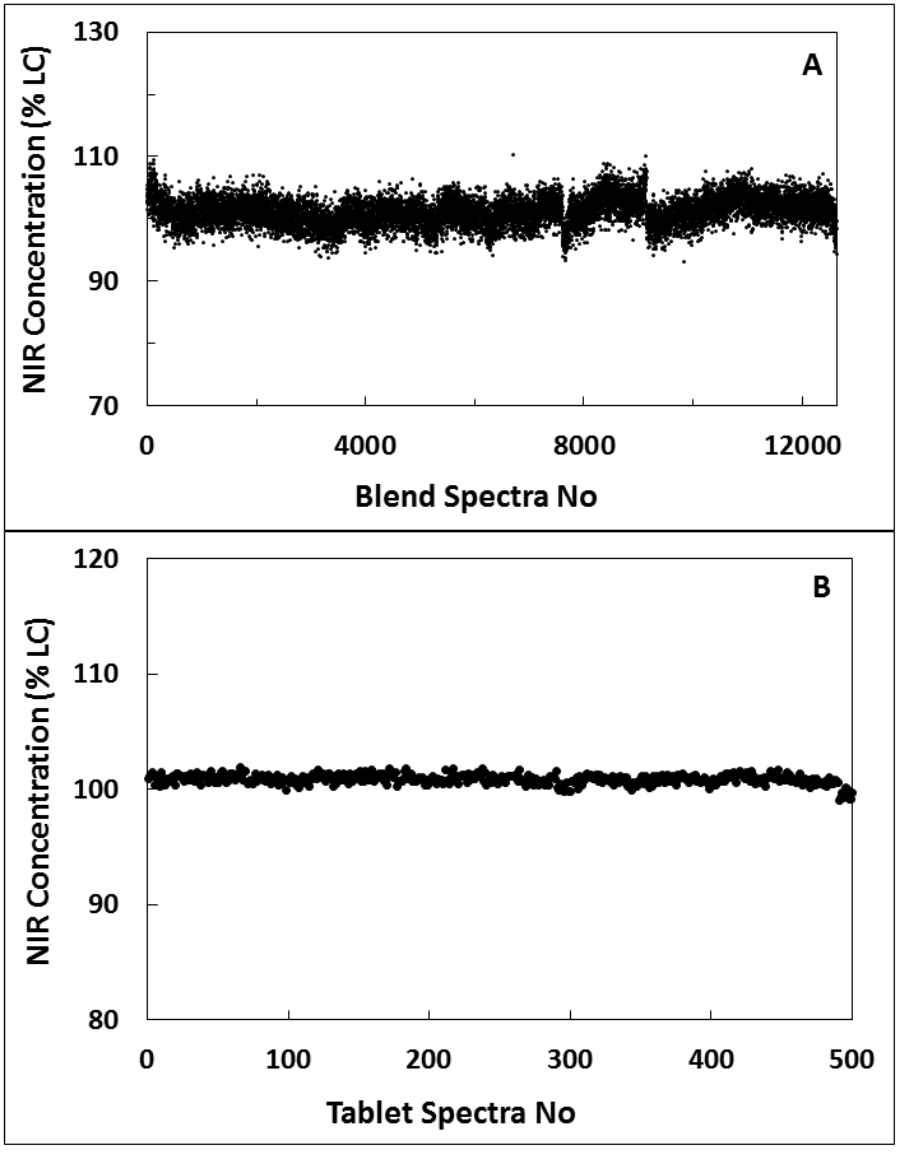

**25 spectra of flowing blends at 70, 85, 100, 115, and 130% LC.**

**Two blends at 100% LC, using different batches of API.**

**Total of 150 calibration spectra.**

**82 kg used to prepare the calibration & validation sets.**

# NIR Monitoring of Continuous Mixing




101.17% LC, SD= 2.17% (n=12,633). Blends by NIRS

100.86% LC, SD = 0.40% n = 500 tablets by Transmission NIRS.

Vargas, J. M.; Nielsen, S.; Cárdenas, V.; Gonzalez, A.; Aymat, E. Y.; Almodovar, E.; Classe, G.; Colón, Y.; Sanchez, E.; Romañach, R. J., Process analytical technology in continuous manufacturing of a commercial pharmaceutical product. *Int. J. Pharm.* 2018, *538* (1–2), 167-178.

# Feed Frame in Compressing Maching

ENGINEERING RESEARCH CENTER FOR
STRUCTURED ORGANIC PARTICULATE SYSTEMS
RUTGERS UNIVERSITY
PURDUE UNIVERSITY
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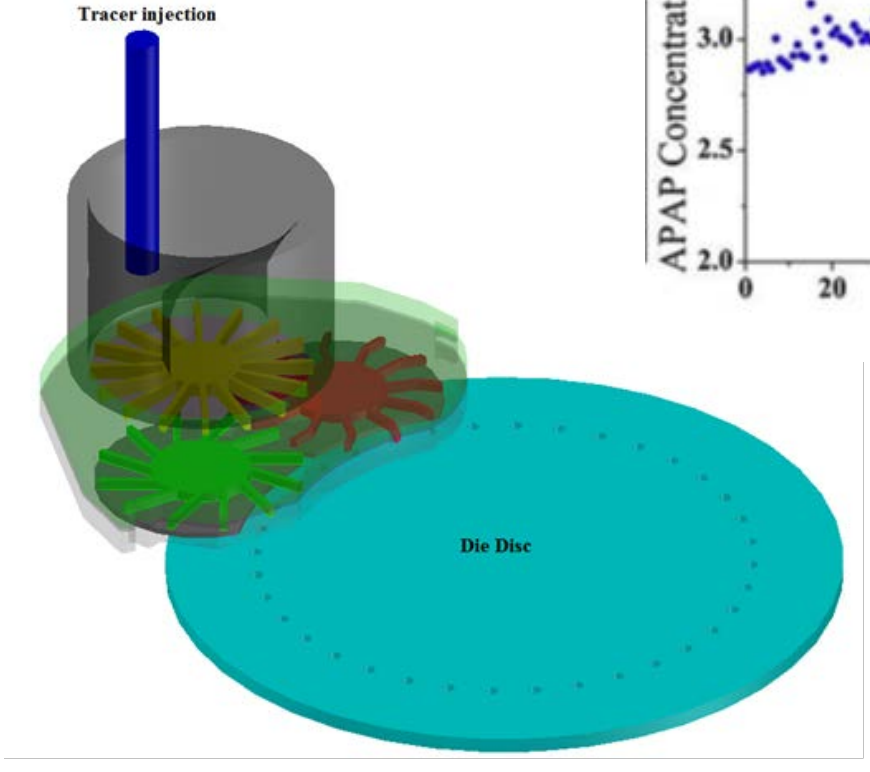
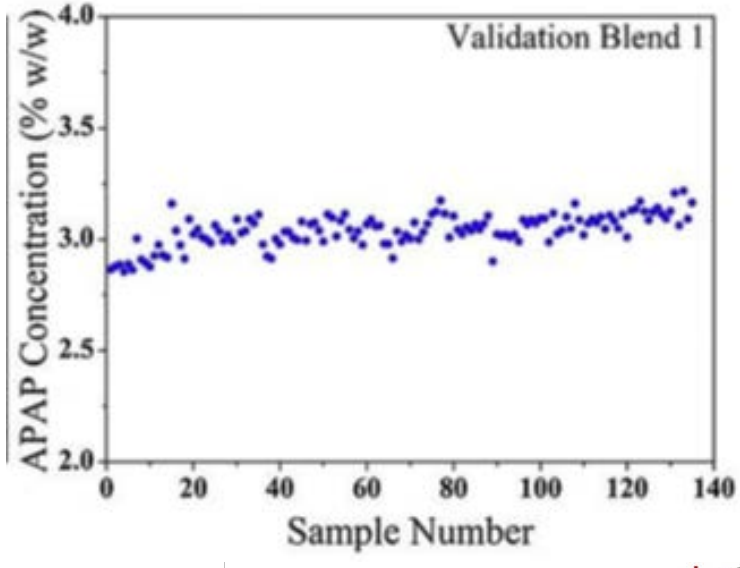
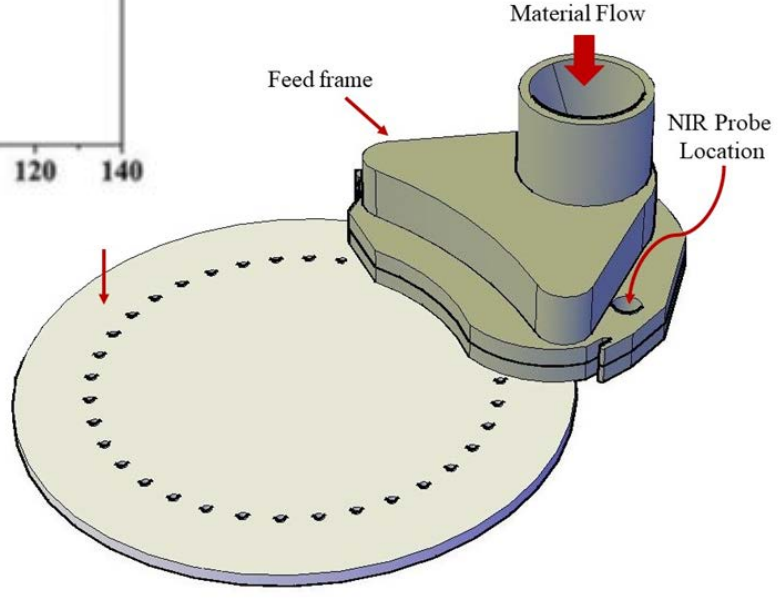
UNIVERSITY OF PUERTO RICO AT MAYAGÜEZ




**Sierra-Vega, N. O.; Sánchez-Paternina, A.; Maldonado, N.; Cárdenas, V.; Romañach, R. J.; Méndez, R., In line monitoring of the powder flow behavior and drug content in a Fette 3090 feed frame at different operating conditions using Near Infrared spectroscopy. *J. Pharm. Biomed. Anal.* 2018,** *154*, 384-396.

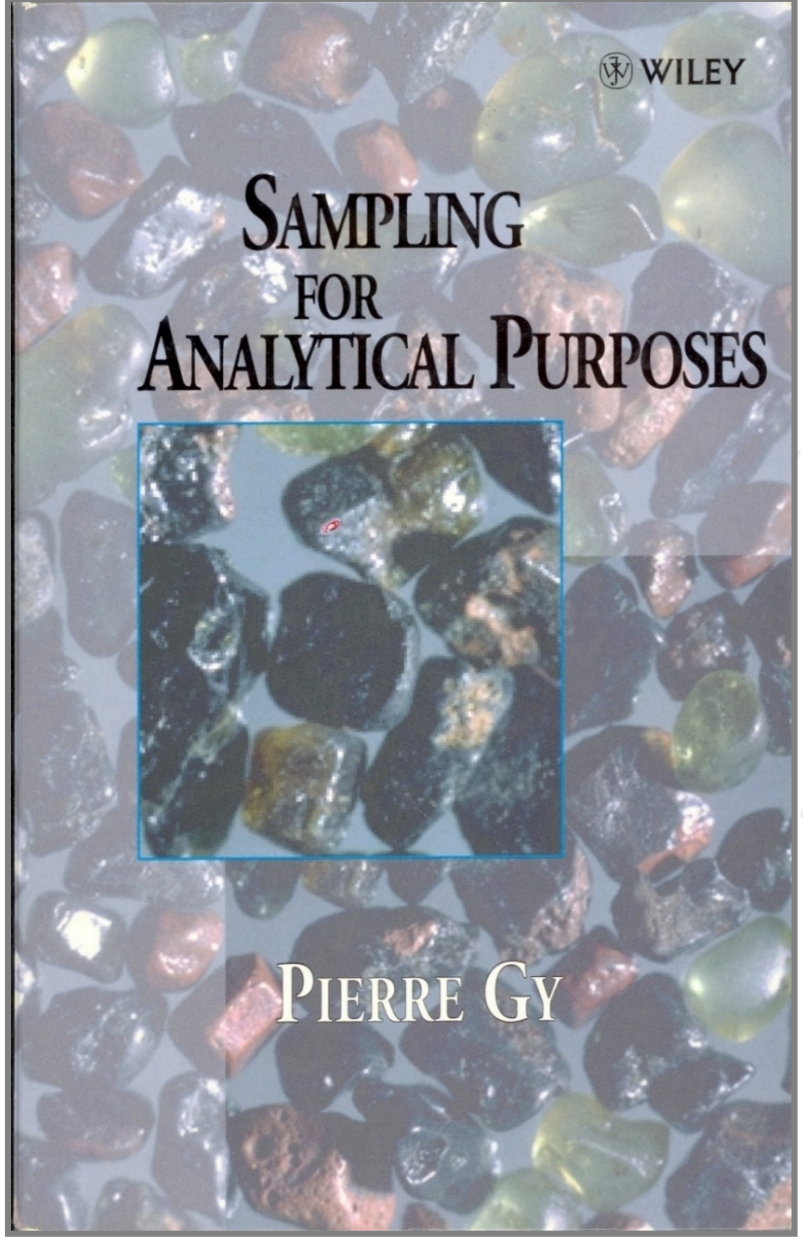
# What would be the Composition a Flowing Powder if it is Analyzed Again?

**Could we do a repeatability study for a flowing powder ?**

Challenging since powder is flowing.

Variographic Analysis - Estimate of sampling and analytical variance.

Repeatability study only provides the analytical variance.




"Theory of Sampling (TOS) – A body of theoretical work initiated in 1950 by the French Scientist Pierre Gy, who over a period of 25 years developed a compete theory of heterogeneity, sampling procedures and sampling equipment assessment (design principles, operation, and maintenance requirements."

Danish-Standards-Foundation, DS 3077(2013). In *Representative Sampling - Horizontal Standard*, Danish Standards Foundation: 2013; pp 1- 42.

KHE Consulting **www.kheconsult.com**


Formerly of the Geological Survey of Denmark and Greenland (GEUS)

# Fundamental Sampling Principle

Fundamental Sampling Principle (FSP), which states that all potential elements from any lot must have an equal probability of being sampled, and that samples are not altered in any way after the sampling process

**Esbensen, K. H.; Romañach, R. J.; Román-Ospino, A. D., Chapter 4 - Theory of Sampling (TOS): A Necessary and Sufficient Guarantee for Reliable Multivariate Data Analysis in Pharmaceutical Manufacturing A2 - Ferreira, Ana Patricia. In *Multivariate Analysis in the Pharmaceutical Industry*, Menezes, J. C.; Tobyn, M., Eds. Academic Press: 2018; pp 53-91.**

# Fundamental Sampling Principle (FSP)  3-D lot

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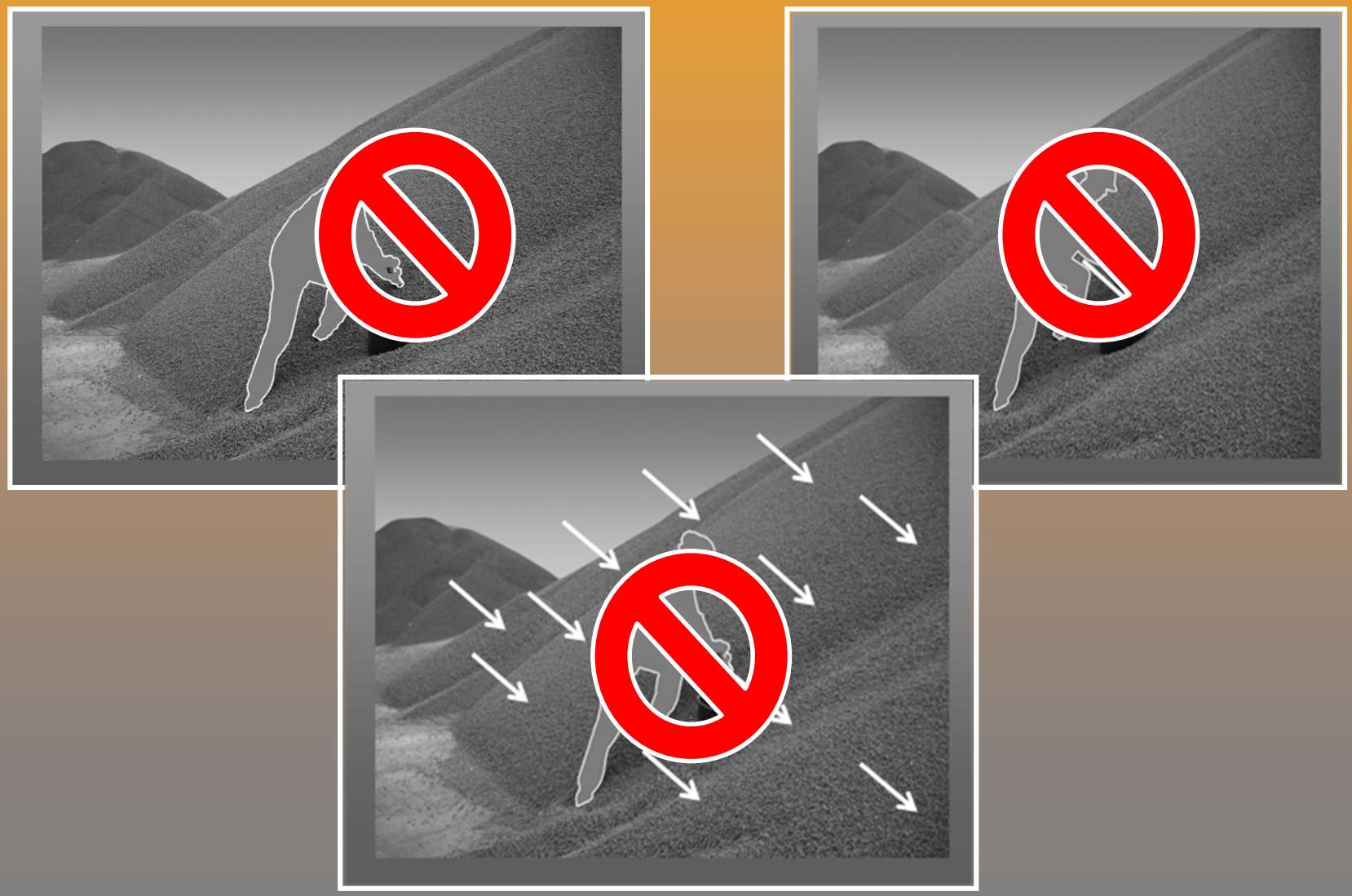
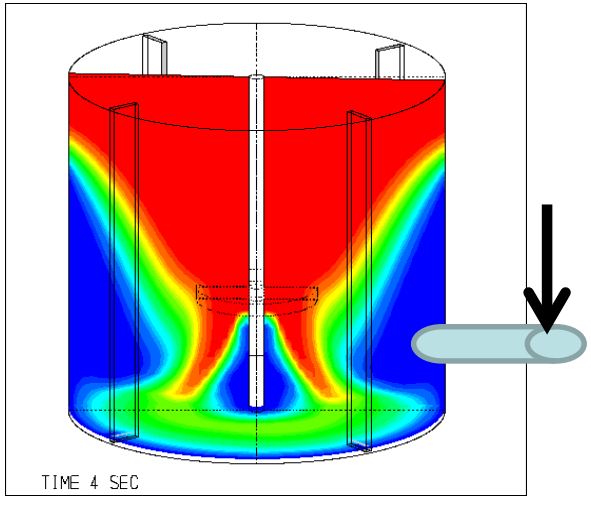
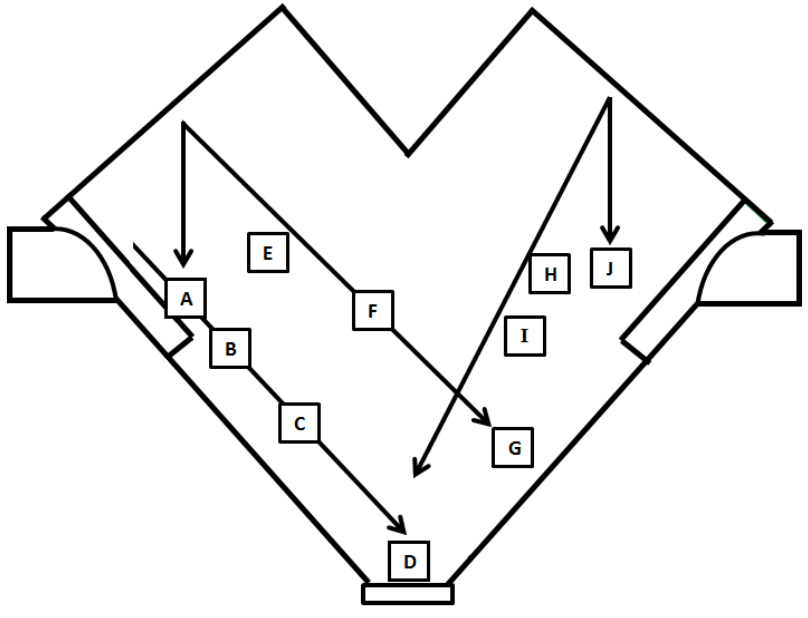


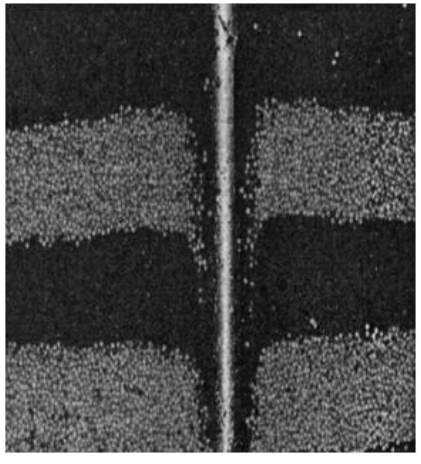
# Correct vs. Incorrect Selection

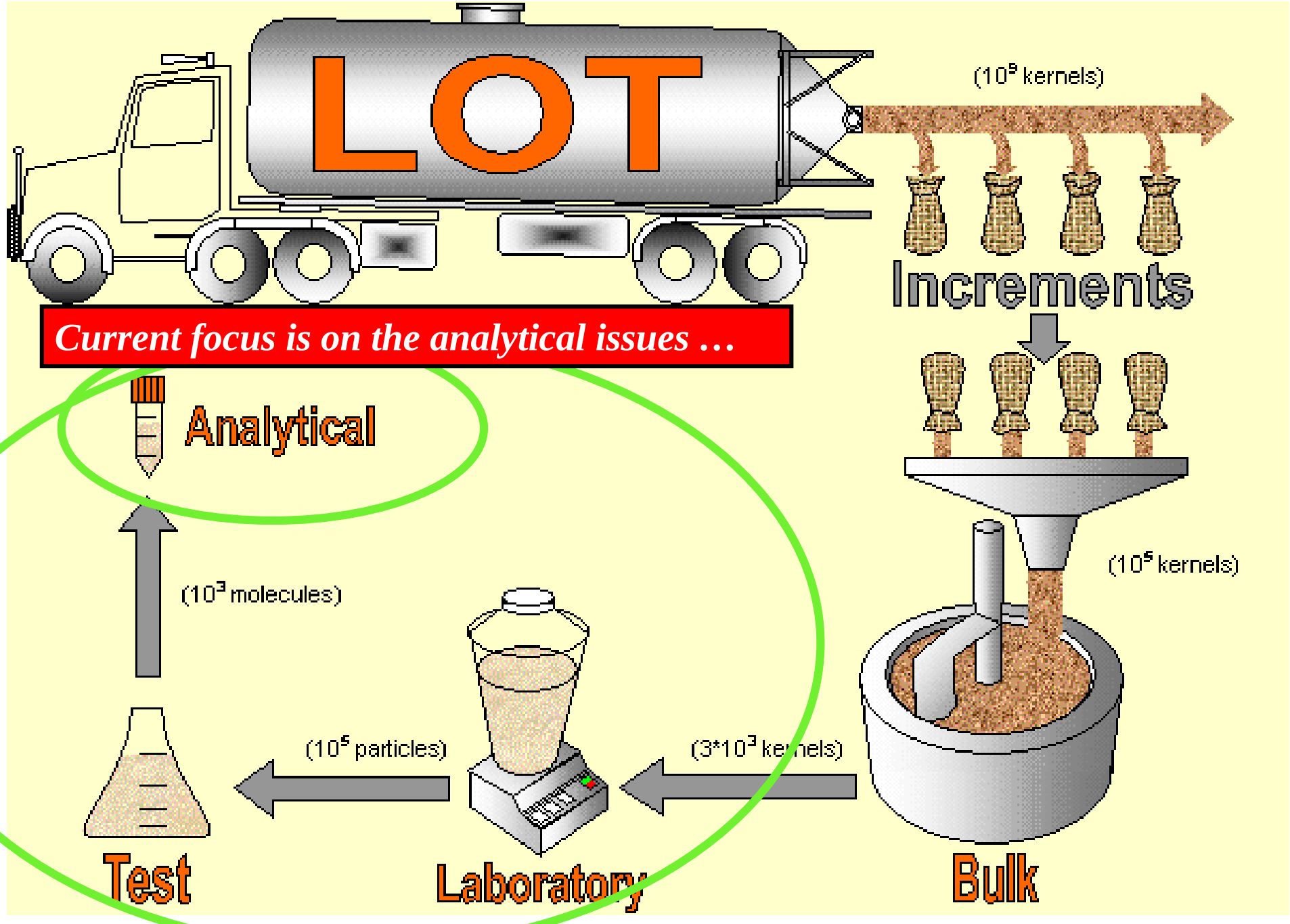
**A probabilistic selection can be:**

**<u>Correct</u> – “when all the constituent elements of the lot to be evaluated have an equal probability of being taken into the sample”. & “when the increments and the sample are not affected in any way”.**



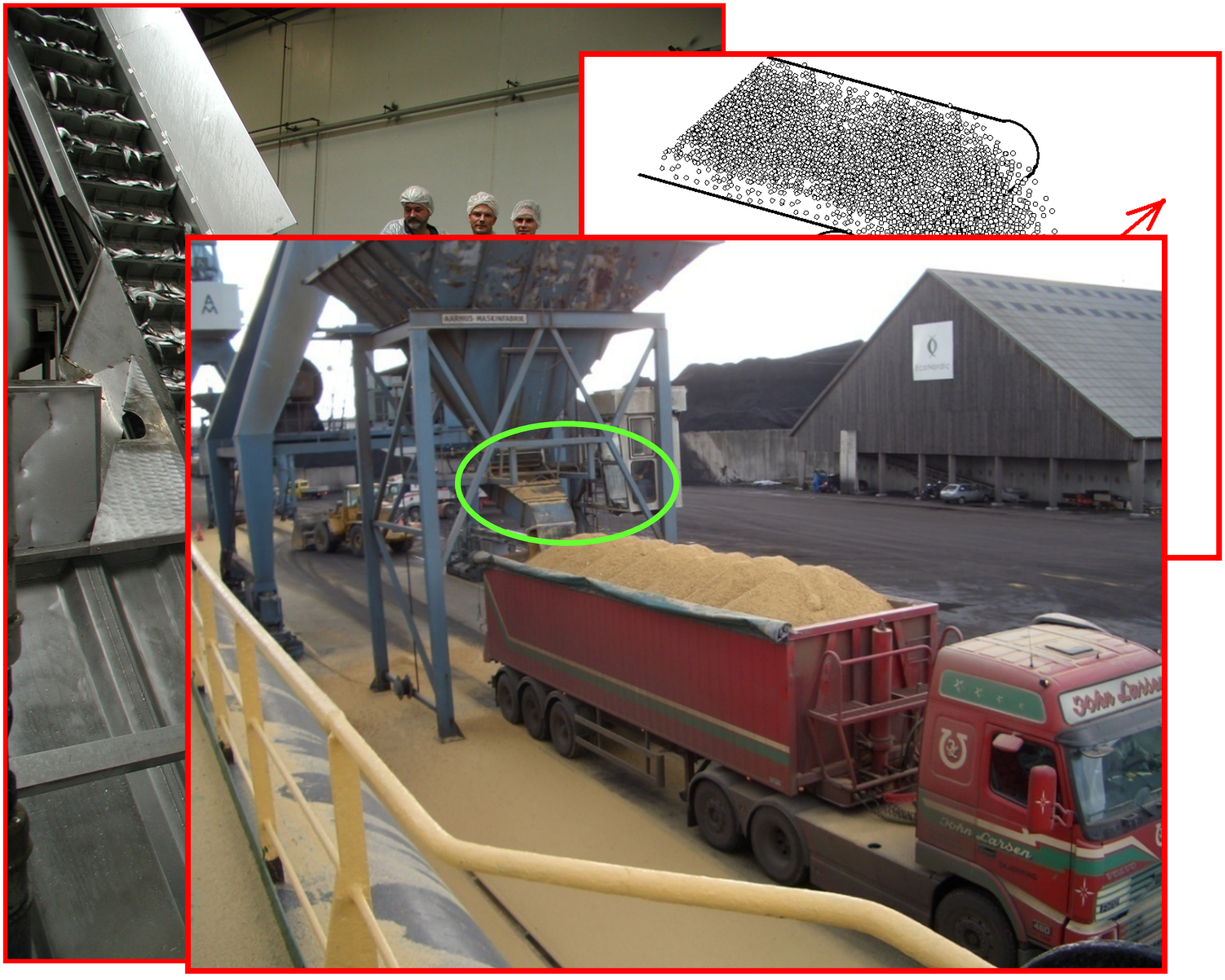



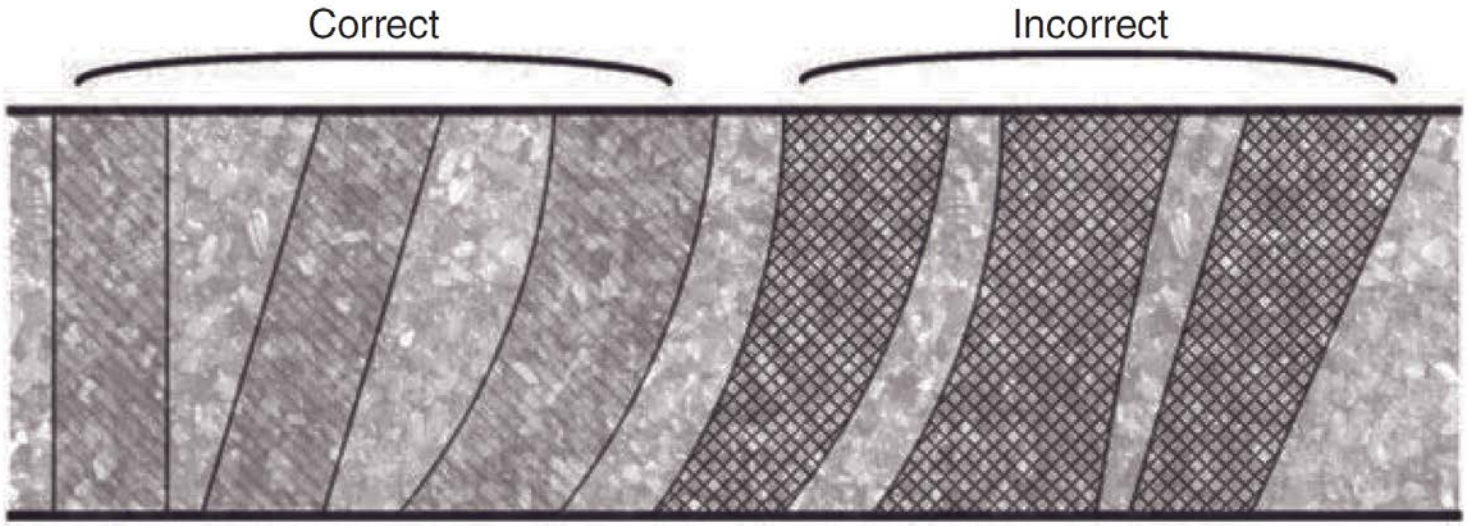

LOT
($10^8$ kernels)
Increments
Current focus is on the analytical issues …
Analytical
($10^3$ molecules)
($10^5$ kernels)
($10^5$ particles)
($3*10^3$ kernels)
Test
Laboratory
Bulk

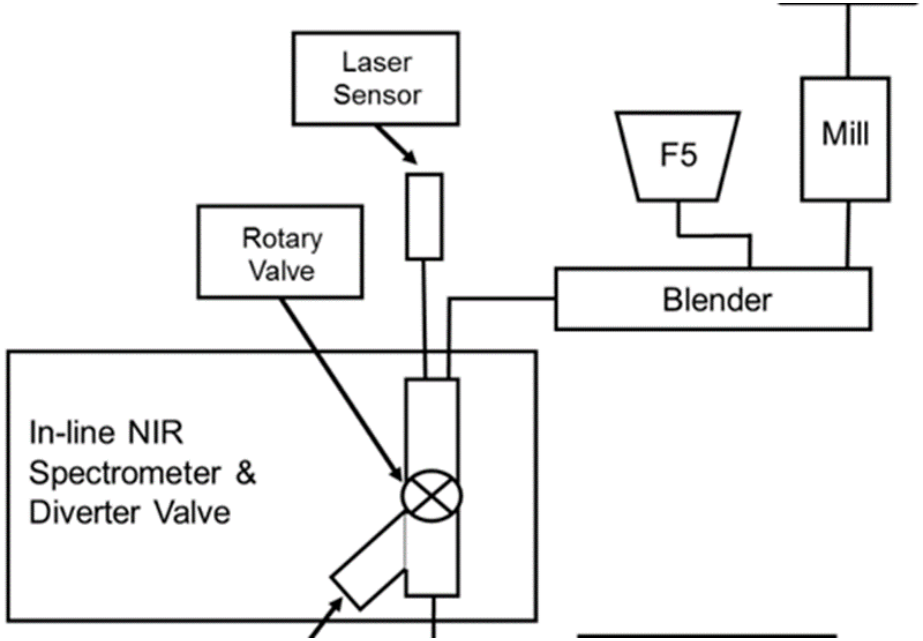
# LDT: Lot dimensionality transformation

**Petersen, L.; Minkkinen, P.; Esbensen, K. H., Representative sampling for reliable data analysis: Theory of Sampling. *Chemometrics Intellig. Lab. Syst.* 2005, *77* (1–2), 261-277.**


AARHUS MASKINFABRIK
John Larsen

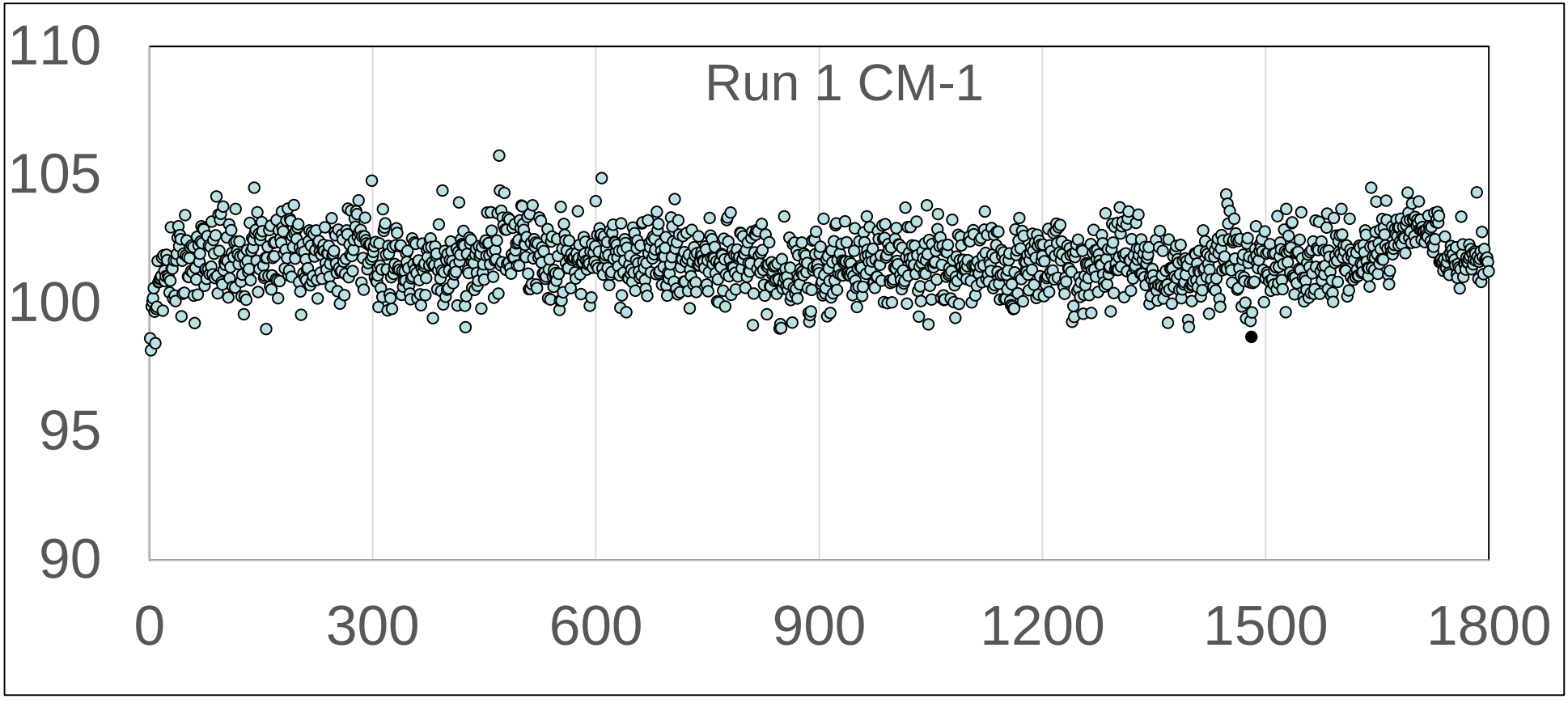
# Increment Delimitation Error



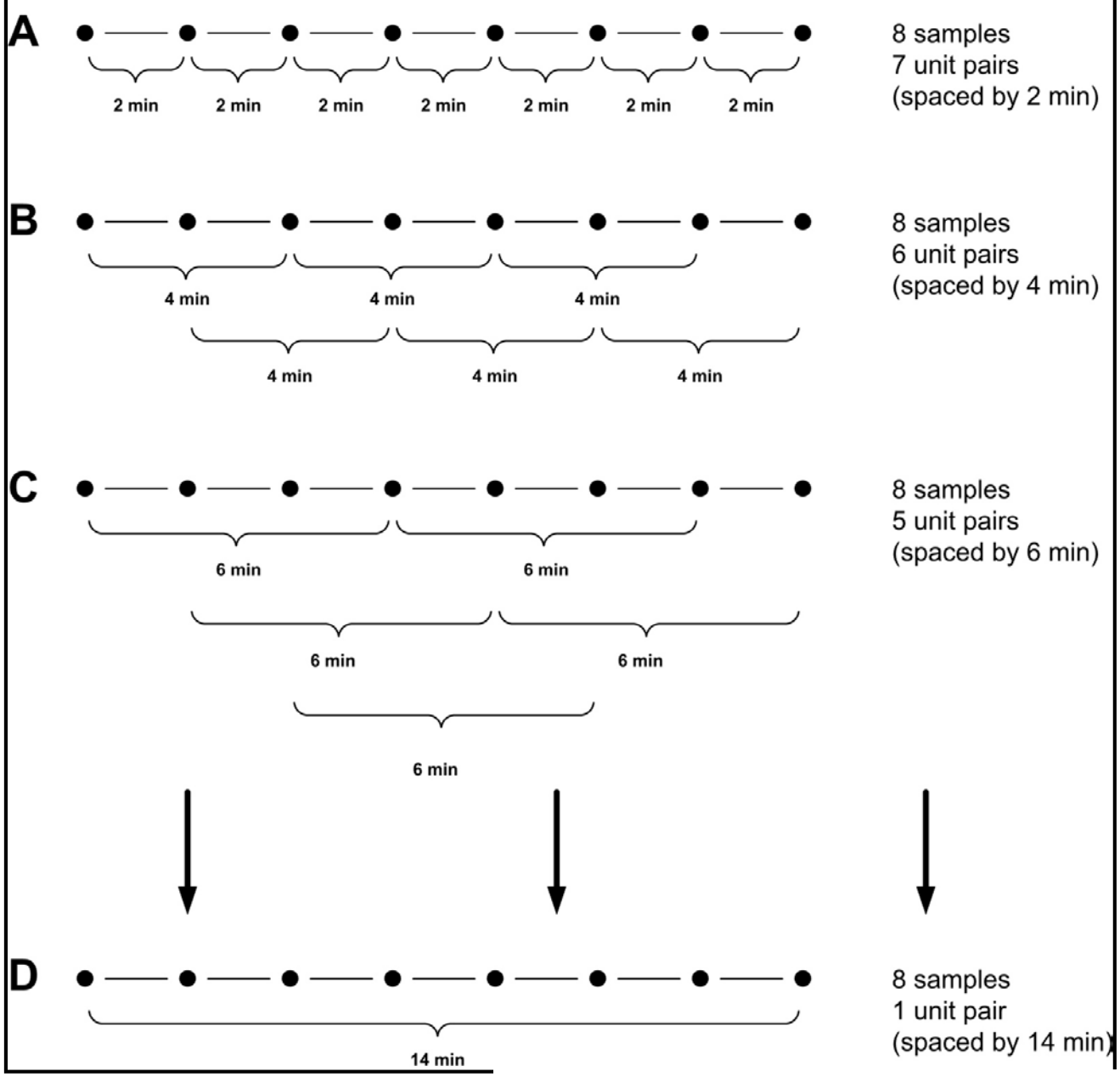

Fundamental Sampling Principle (FSP), which states that all potential elements from any lot must have an equal probability of being sampled, and that samples are not altered in any way after the sampling process.

## Knowing the order of samples makes variographic analysis possible – obtain an estimate of the sampling and analytical errors -- 2.5 hour run (1800 spectra)




## Avg = 101.67% of label, Std Dev. = 0.97

*Journal of Pharmaceutical Innovation, 2017, 12*(2), 155–167.



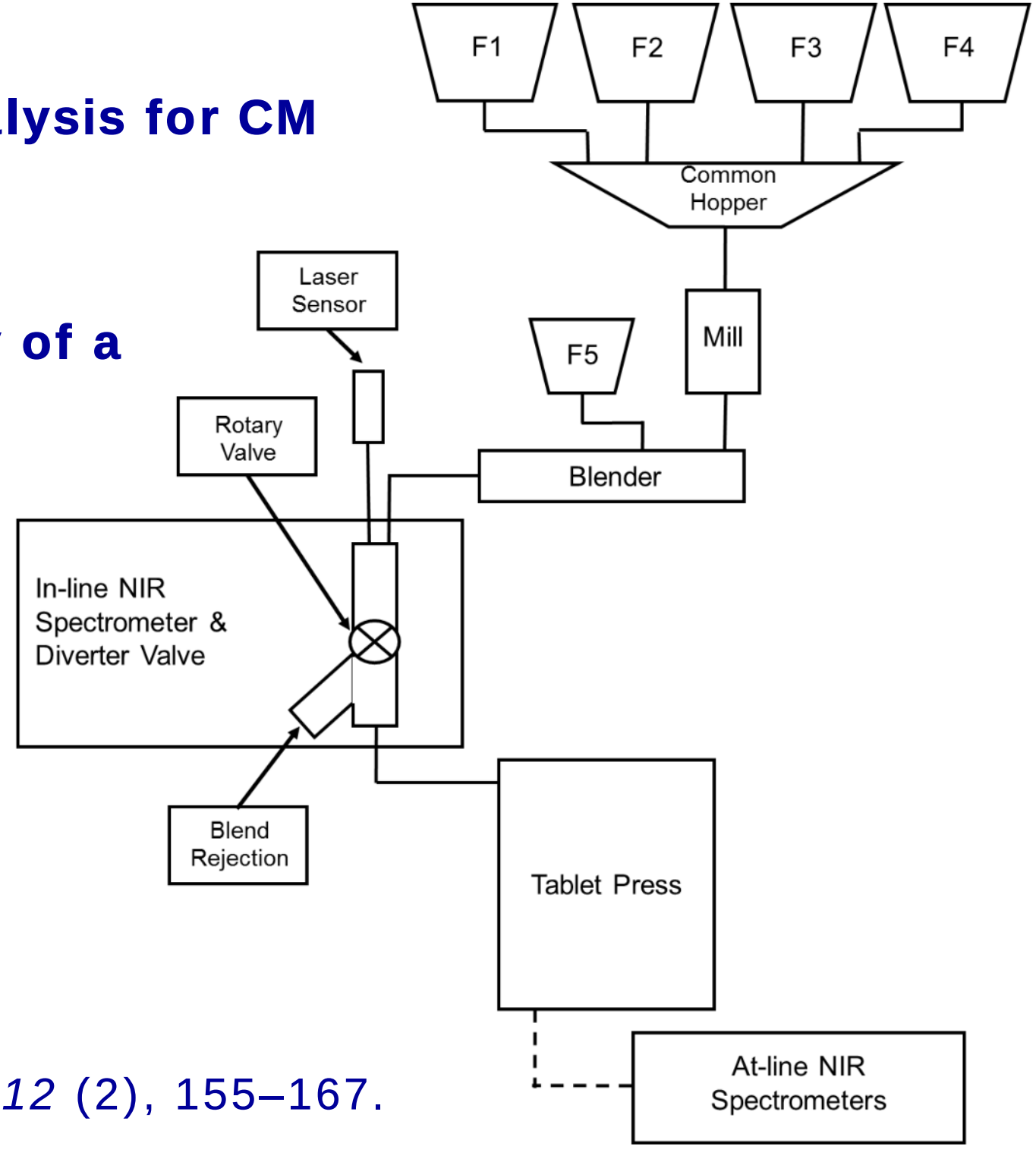

$$j = \frac{\theta}{\theta_{min}}$$

**$N_U$ = total number of data points**

$$V(j) = \frac{1}{2(Q_{total} - j)} \sum_{q=1}^{Q_{total}-j} (h_{q+j} - h_q)^2$$

# Variographic Analysis for CM

## Continuous Mfg NIR Spectroscopy of a Flowing Powder

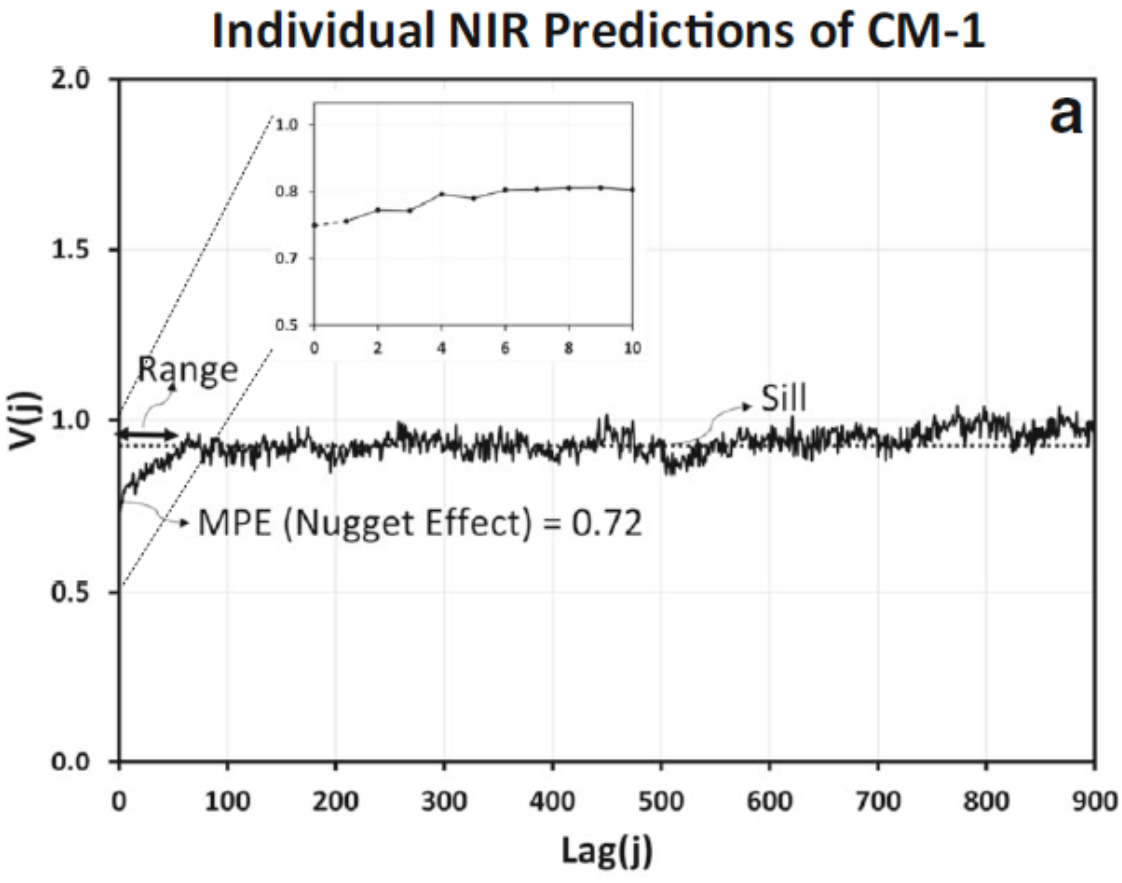



*J Pharm Innov* 2017, *12* (2), 155–167.

# Computing Variograms – Slide by Andres Roman, Ph.D.

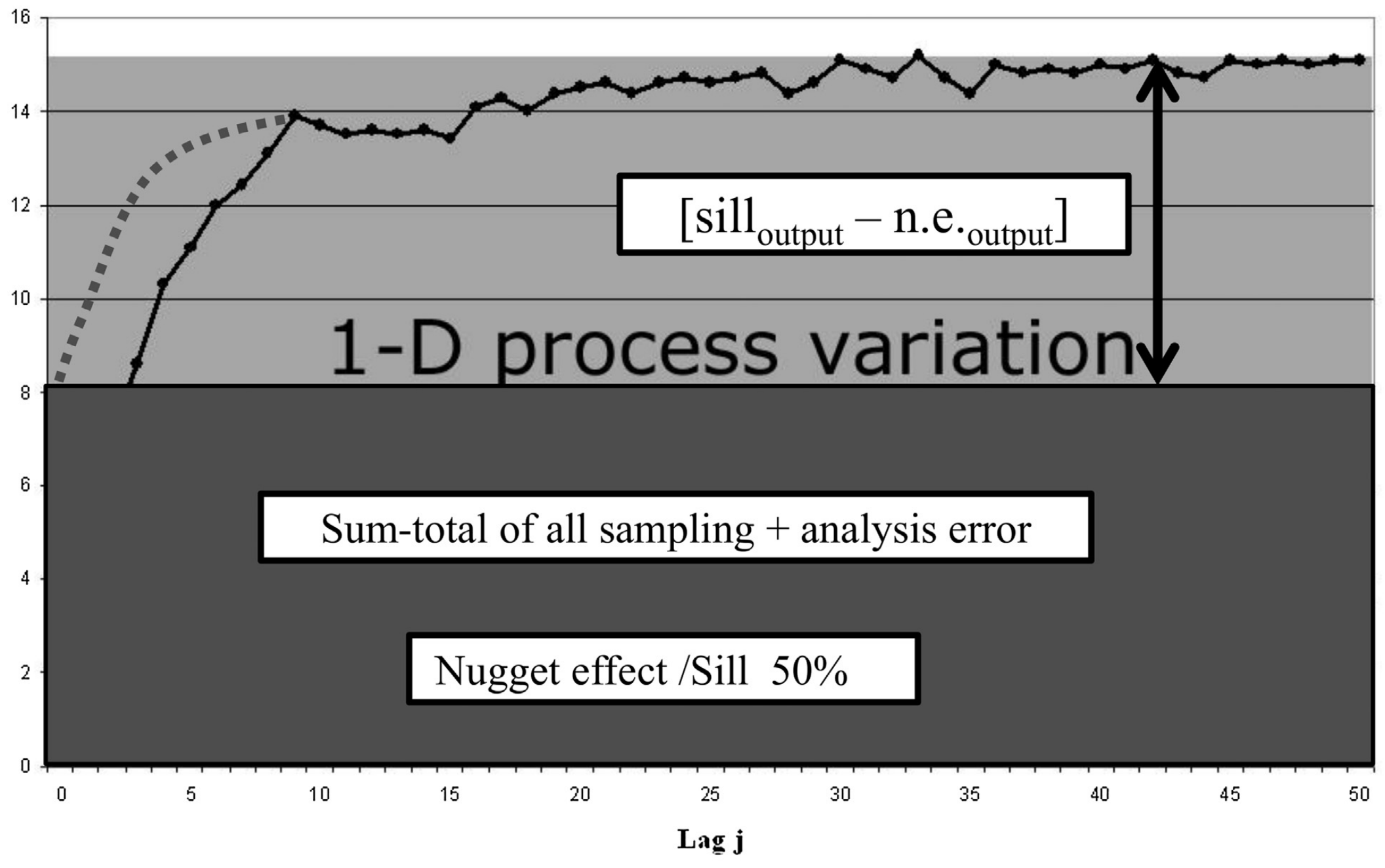
| | B | C | D | E | F | G | H | I | J | K | L | M |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Hq (Pred Values) | Lag (j) | V(j) | Q-j | 1/(2(Q-j)) | sum(hq+j-hq)^2 | Lag1 | Lag2 | Lag3 | Lag4 | Lag5 | Lag6 |
| 2 | | | | | | | | | | | | |
| 3 | **15.04** | 1 | 0.245 | 207 | 0.002 | 102 | 0.00214 | 0.21641 | 0.15936 | 0.04268 | 0.64609 | 2.13949 |
| 4 | **14.99** | 2 | 0.409 | 206 | 0.002 | 169 | 0.17548 | 0.12454 | 0.06396 | 0.57381 | 2.00619 | 1.34351 |
| 5 | **14.57** | 3 | 0.455 | 205 | 0.002 | 186 | 0.00436 | 0.45132 | 0.11465 | 0.99501 | 0.5479 | 1.09161 |
| 6 | **14.64** | 4 | 0.490 | 204 | 0.002 | 200 | 0.36699 | 0.1637 | 1.13103 | 0.64996 | 0.95805 | 3.47114 |
| 7 | **15.24** | 5 | 0.573 | 203 | 0.002 | 233 | 1.02091 | 2.78656 | 1.99374 | 0.13913 | 1.5808 | 0.07054 |
| 8 | **14.23** | 6 | 0.638 | 202 | 0.002 | 258 | 0.43415 | 0.16128 | 1.9138 | 5.14246 | 1.62818 | 0.74909 |
| 9 | **13.58** | 7 | 0.652 | 201 | 0.002 | 262 | 0.0662 | 4.17099 | 8.56499 | 3.74384 | 2.3238 | 3.2436 |
| 10 | **13.83** | 8 | 0.668 | 200 | 0.003 | 267 | 3.18623 | 7.12516 | 2.81434 | 1.60554 | 2.38301 | 5.35876 |
| 11 | **15.62** | 9 | 0.699 | 199 | 0.003 | 278 | 0.78199 | 0.01153 | 0.26822 | 0.05823 | 0.28079 | 1.30599 |
| 12 | **16.50** | 10 | 0.730 | 198 | 0.003 | 289 | 0.98347 | 1.96616 | 1.26698 | 0.1256 | 4.10913 | 6.36351 |
| 13 | **15.51** | 11 | 0.699 | 197 | 0.003 | 275 | 0.16851 | 0.01793 | 0.40615 | 1.07205 | 2.34365 | 2.22189 |
| 14 | **15.10** | 12 | 0.708 | 196 | 0.003 | 277 | 0.07651 | 1.09788 | 0.3905 | 1.2553 | 1.16662 | 1.67314 |
| 15 | **15.38** | 13 | 0.745 | 195 | 0.003 | 291 | 0.59475 | 0.8127 | 1.95161 | 1.84063 | 2.46521 | 3.23137 |
| 16 | **16.15** | 14 | 0.750 | 194 | 0.003 | 291 | 2.79793 | 4.70109 | 4.52796 | 5.48169 | 6.59873 | 3.62027 |

$$V(j) = \frac{1}{2(Q_{total} - j)} \sum_{q=1}^{Q_{total}-j} \left(h_{q+j} - h_q\right)^2$$




- MPE - estimate of the total sampling error and the total analytical error. Calculated by extrapolating V(j) to intercept the Y-axis, to estimate "lag 0".
- Sill - gives information about the maximum heterogeneity between samples (total process variation) including sampling and analytical errors.
- Corrected sill - represents the true process variation, or residual variance in the blend after subtracting the nugget effect (MPE) from the sill.

The lower the corrected sill, the closer to reach the final state of blending.

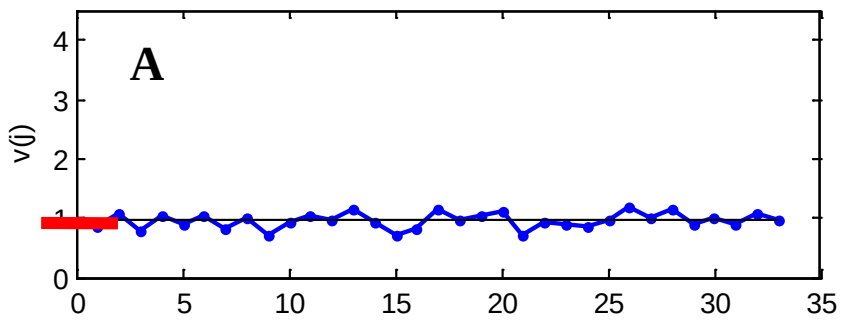



***Int. J. Pharm.* 2016,** *499* (1–2), 156-174.

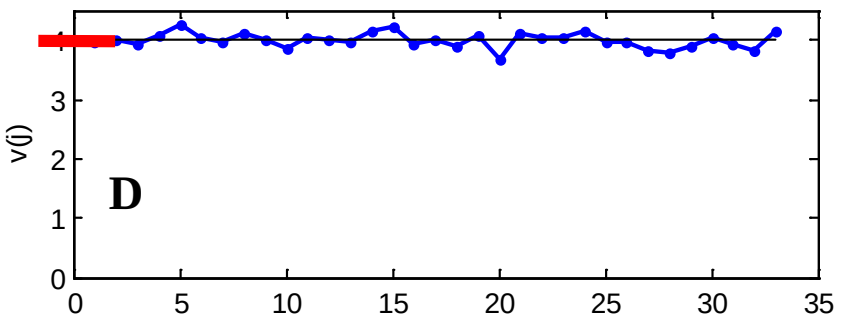
**Variogram: a power**

# Unparalelled corporate QC / QA tool !!!

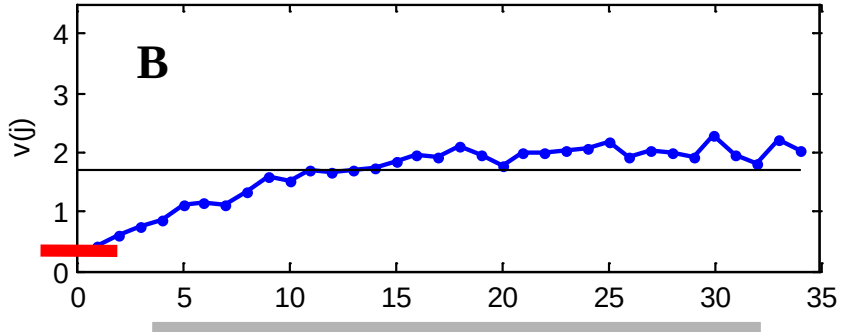
**LOW SILL – Process stable & OK**



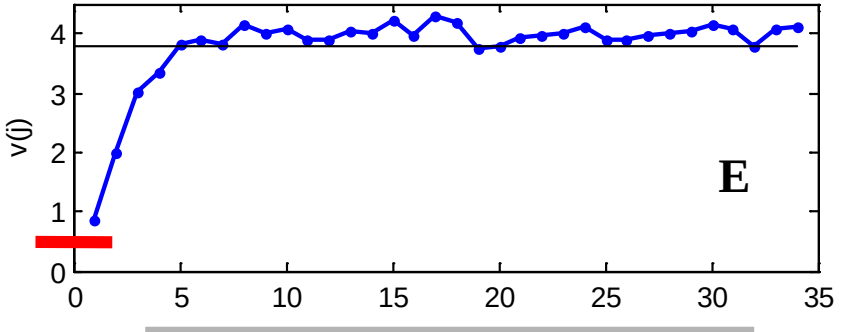

**EXTREMELY HIGH SILL – ;-( ;-(**



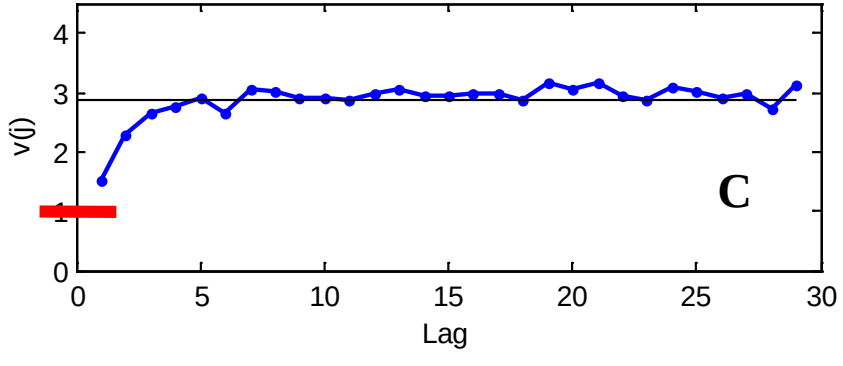

**INTERM./LOW SILL – low n,e,**



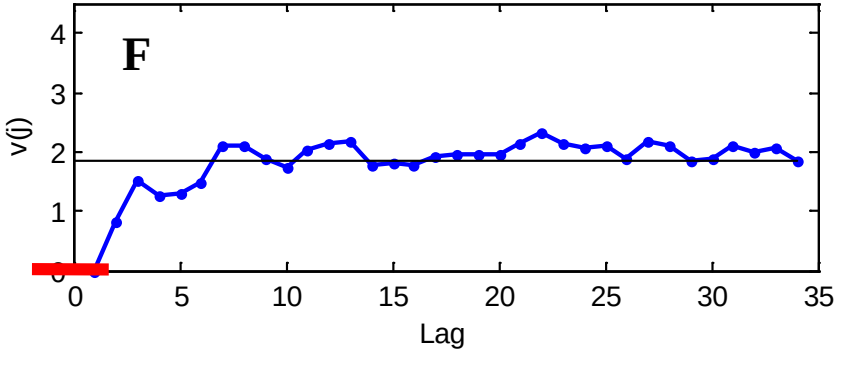

**VERY HIGH SILL – very low n.e.**

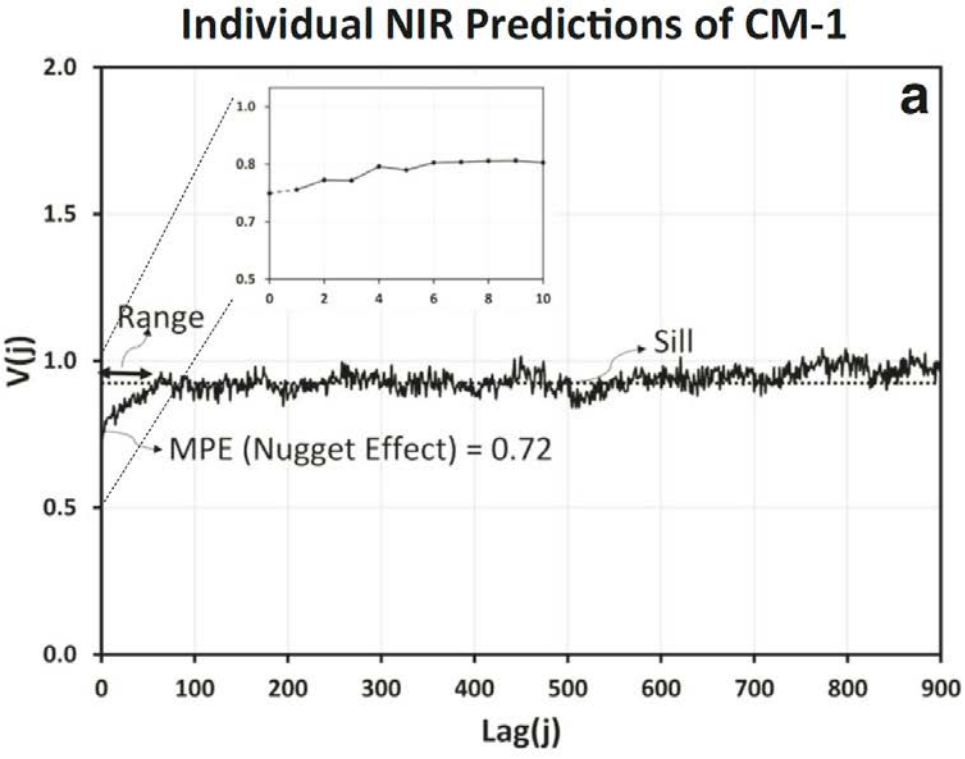



**INTERMEDIATE SILL – low n,e,**

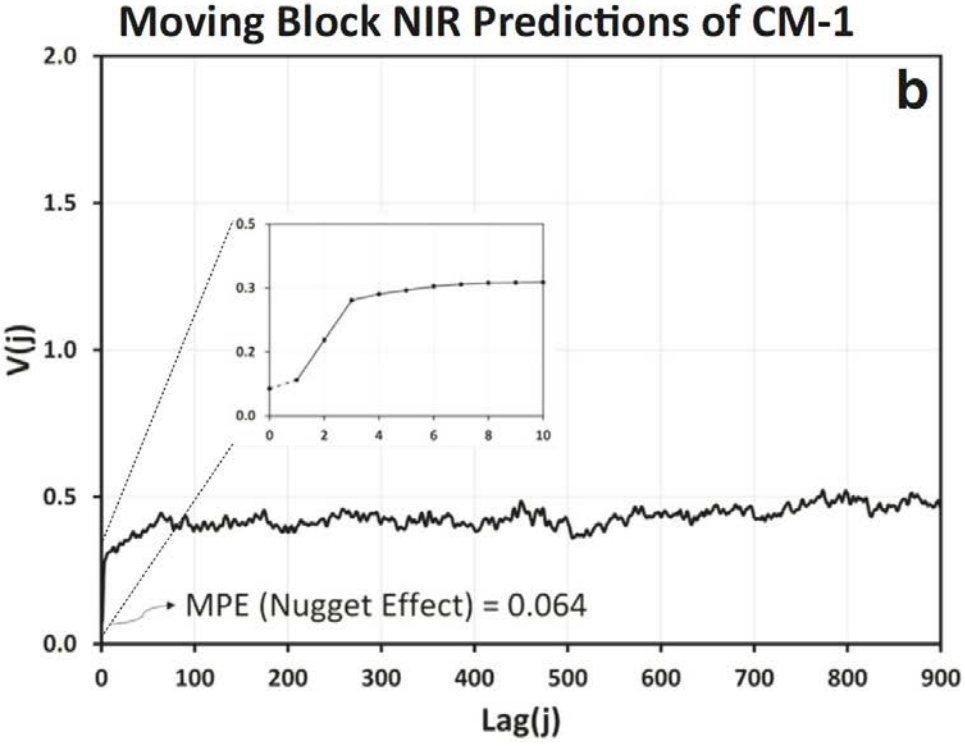



**INTERM./LOW SILL – low n,e,**



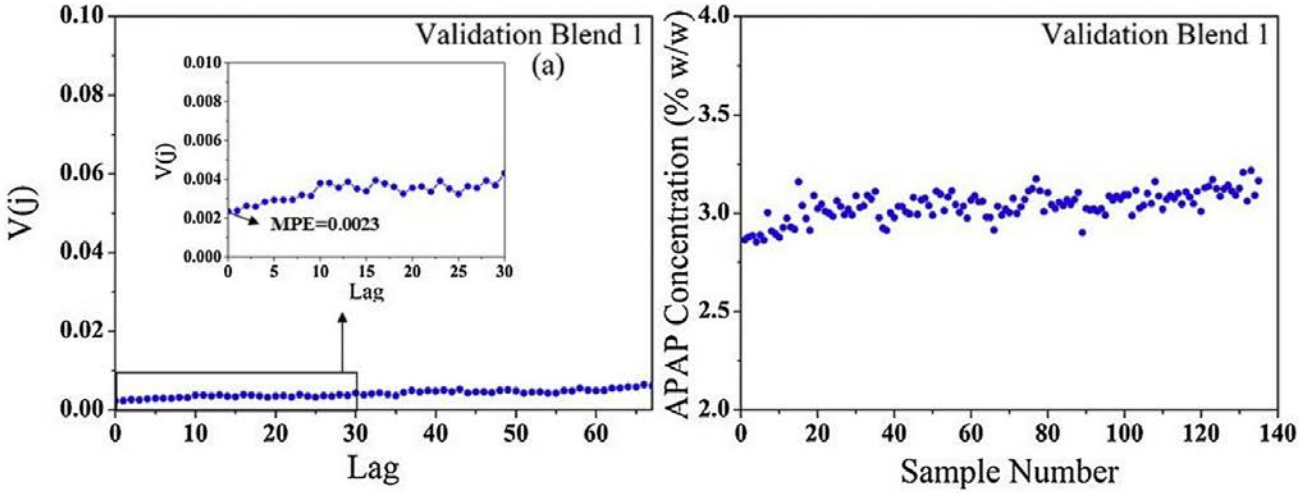


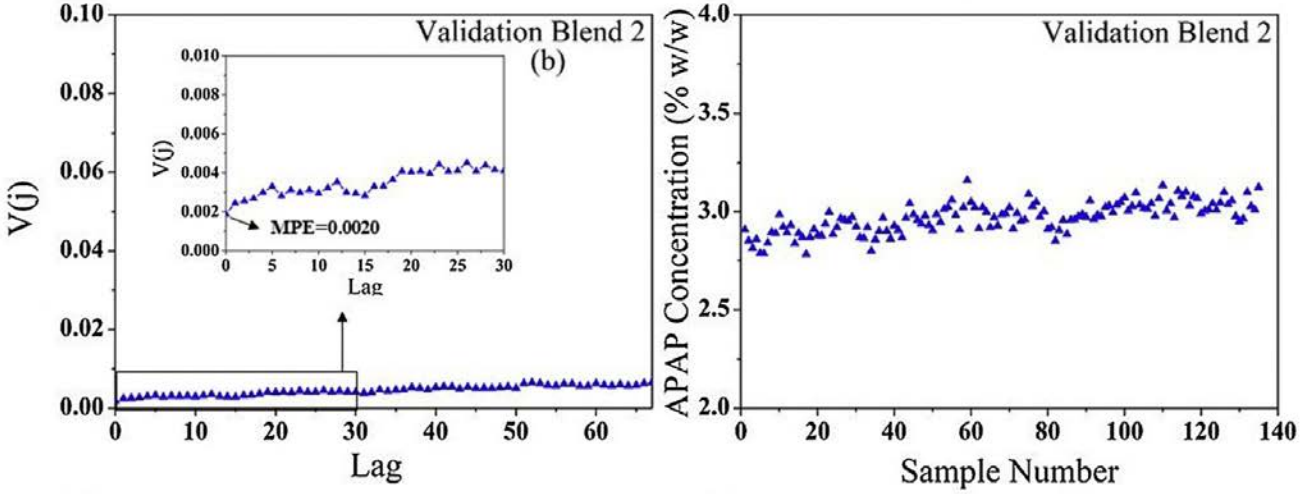

**Sample mass ≈ 37 mg**

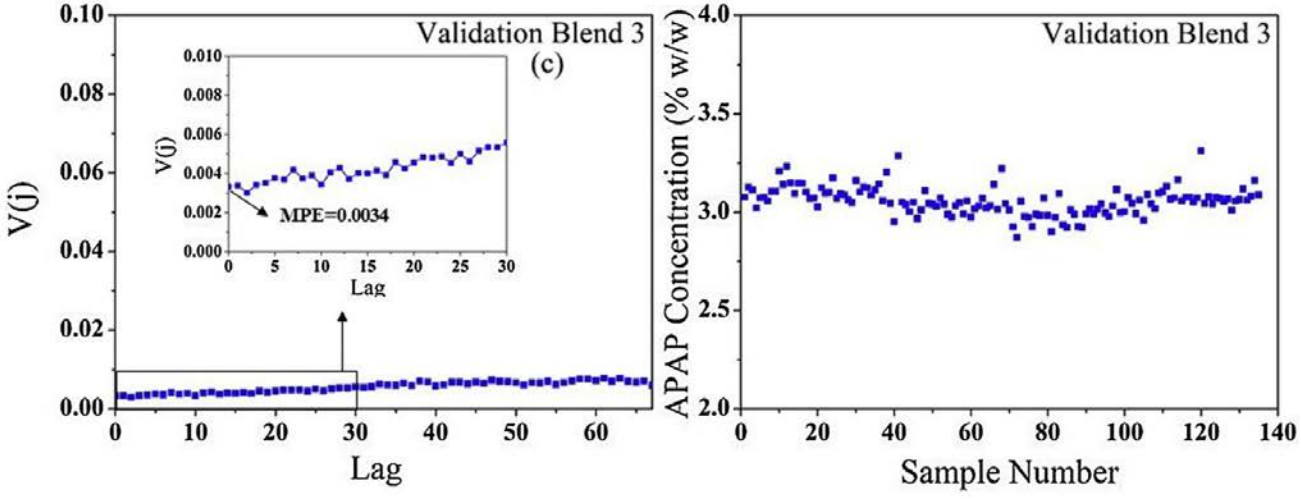


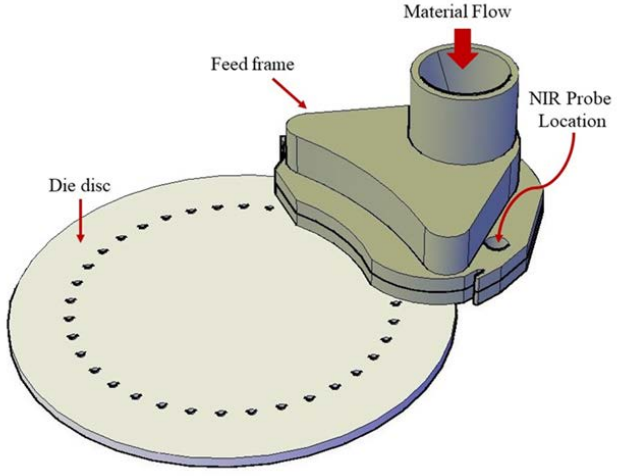

**Sample mass ≈ 110 mg**

***J Pharm Innov* 2017,** *12* (2), 155–167.



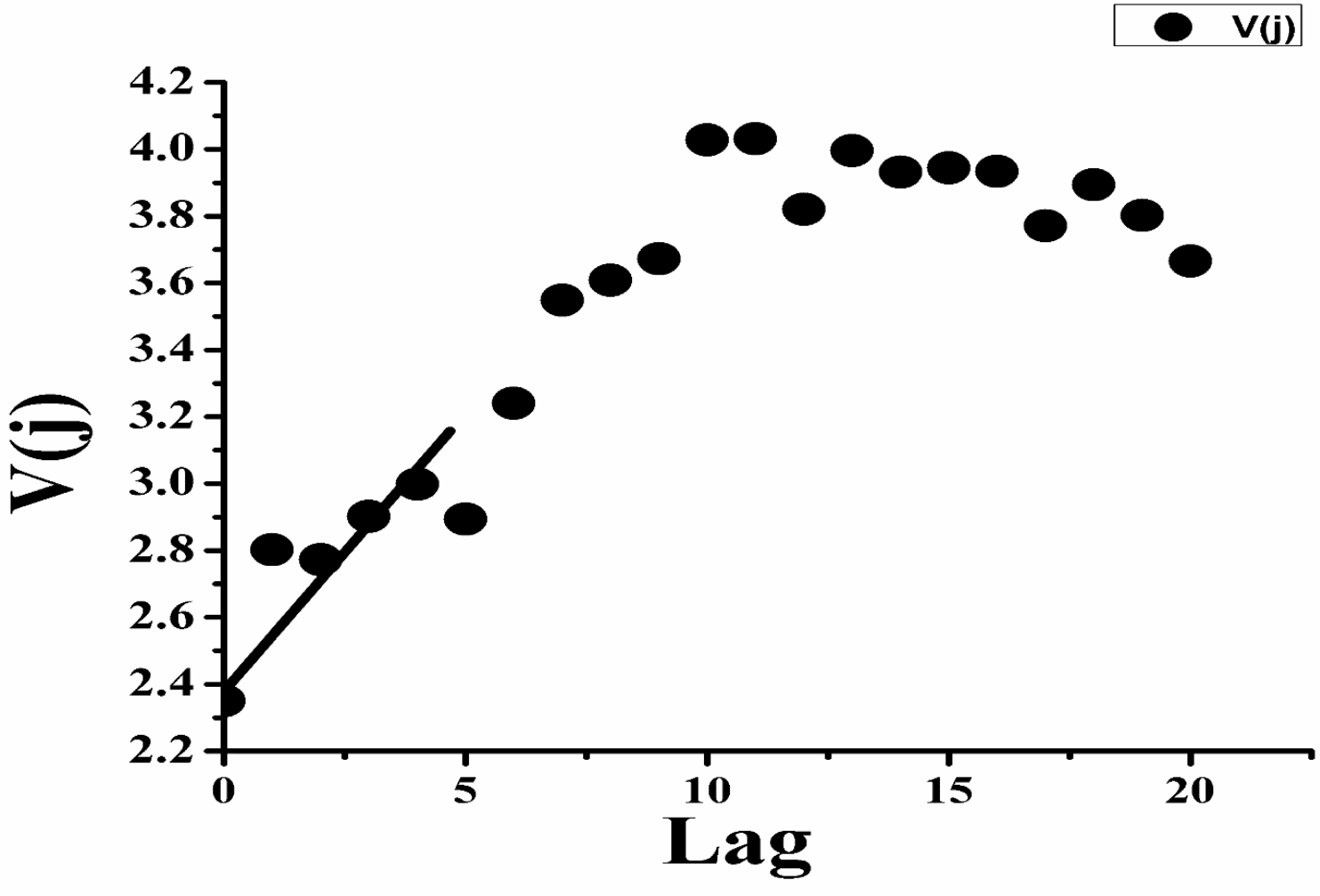




*J. Pharm. Biomed. Anal.* 2018, *154*, 384-396.

# Final Take Home Messages

- Real time monitoring of continuous mfg. makes it possible to use variographic analysis.
- Nugget effect provides an estimate of sampling and analytical errors. This is the only currently available method for estimating the sampling error.
- Variographic could become a very useful method for discern process variation from sampling and analytical errors.
- Excellent BU and CU results were obtained without sample thieves.
- This project is the result of a very fruitful collaboration with Janssen Ortho LLC, and support from Puerto Rico Science Technology & Research Trust and NSF EEC-0540855, I-Corps 1659082 and SBIR 1621688 grants.

# Determination of MPE



# Individual NIR Predictions of CM-1