Biopharmaceutics and Drug Product Quality: Performance Tests for Drug Products, A Look Into the Future

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A Look Into the Future: The future is upon us!

- Increased importance of physical performance characteristics of drug delivery systems
  - Complex drug delivery systems
  - Combination systems (e.g., drug-device)
  - Nanotechnology
- The Science of Quality – a critical dimension is the ability to understand, control, and manage variability

Performance Tests?

- Physical performance
  - Delivery to a site of action (e.g., target organs, tissues and cells)
    - Size, shape, density, (aero or hydro) dynamics, surface chemistry (e.g., charge),…
  - Residence time at the site of action or administration and biological interactions
  - Drug release mechanisms (e.g., passive or triggered)
  - Others

Development of test methods

- Clinical relevance
  - A tool for product development and optimization
  - Establishing clinical relevance
- Quality assurance
  - Batch quality
  - Accuracy and precision
  - Reproducibility and repeatability
  - Reference standards
- Control of variability (e.g., critical quality variables)

Future brings significant challenges

- Lessons from the past and current state?
- What can we learn from dissolution or drug release testing experience?
  - Starting with QA/QC applications
  - Looking back from a manufacturing environment when out of specifications results are observed

OOS or Exceptions Further Increase Cycle Times (Source: G. K. Raju, M.I.T. FDA Science Board Meeting, November 16, 2001)

Pharmaceutical Manufacturing: Impact of Exceptions

(Detailed Analysis of 2 Products)

PERFORMANCE MEASURE	VALUE
• **Average Cycle time**	**95 days**
• **Std dev**(Cycle time)	**> 100 days**
• **Exceptions** increase cycle time by	**> 50 %**
• **Exceptions** increase variability by	**> 100%**
• **Capacity Utilization** of "System"	**LOW**

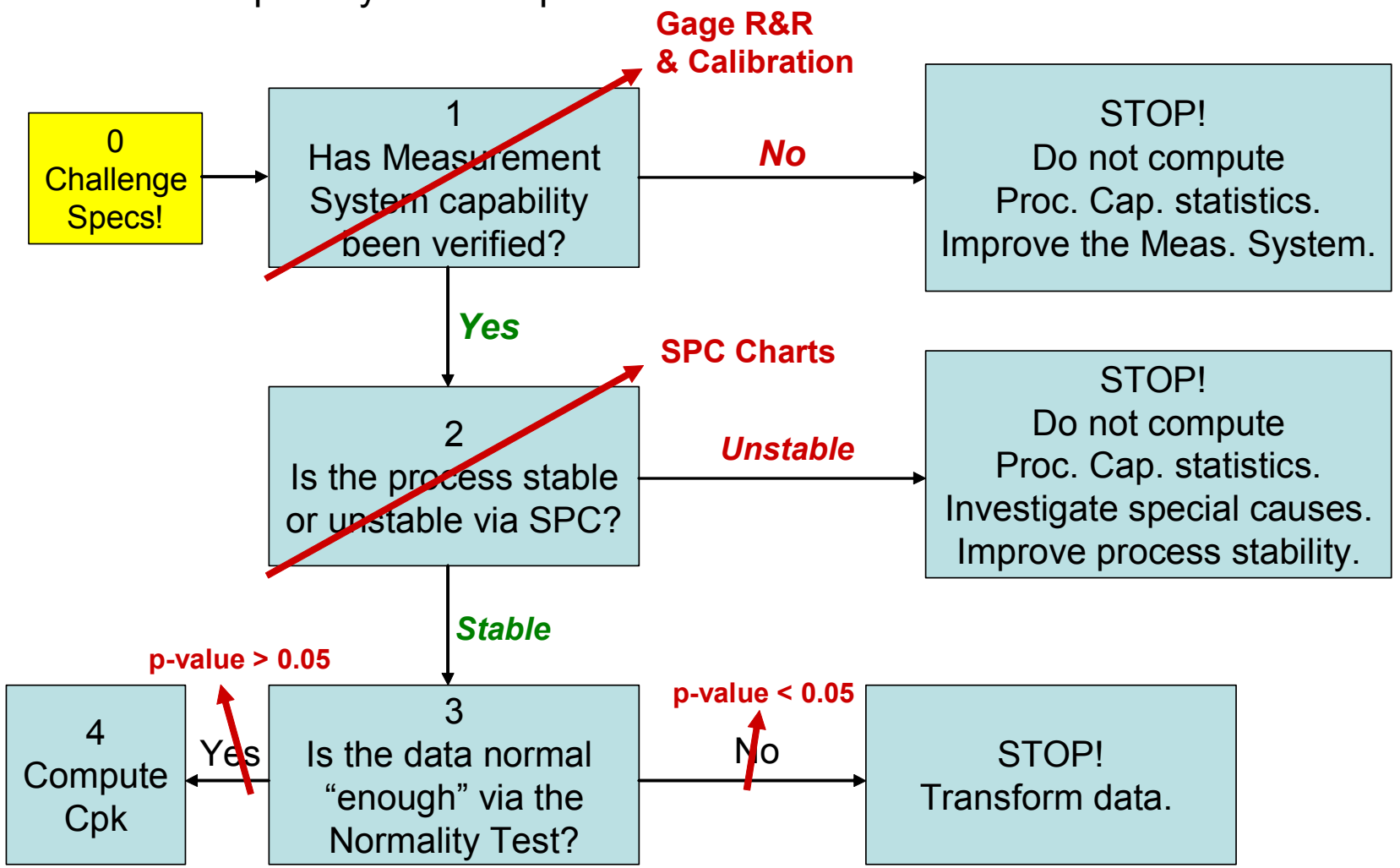
Dissolution

NEED FOR FUNDAMENTAL TECHNOLOGY

Process Capability: If you can't measure it, you can't improve it

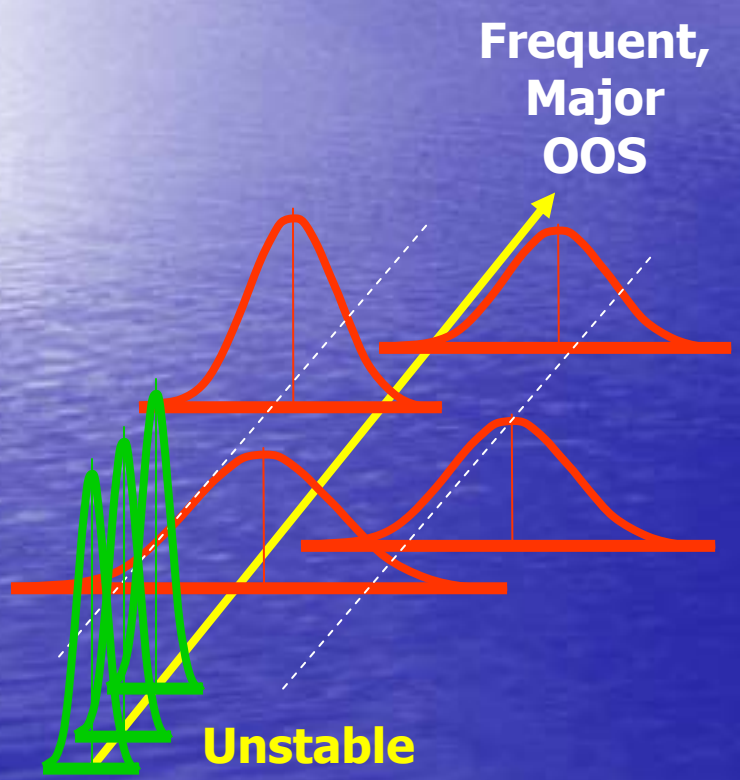
Scott Tarpley, UK Arden House 2004

Process Capability Roadmap:

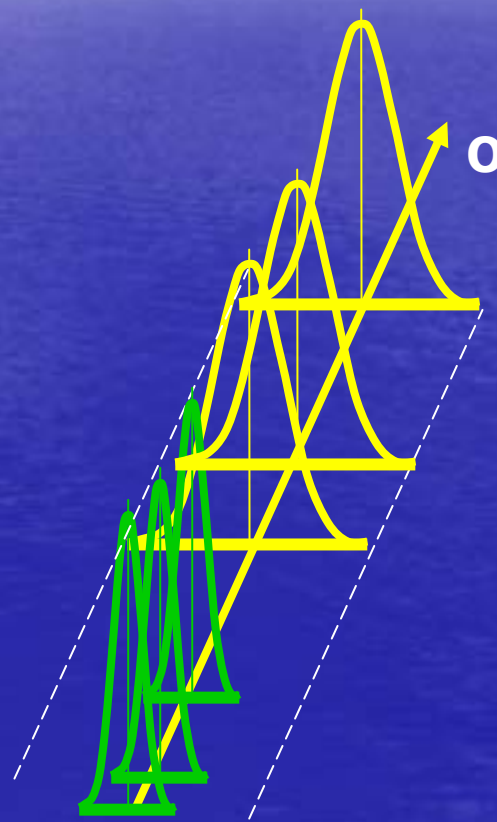


"Special Cause" or "Common Cause"

Corrective Actions
Eliminate "Special Cause"



Reduce "Common Cause"
Variability



Dissolution Experience at the FDA Division of Pharmaceutical Analysis

- Dissolution testing with USP Apparatus 1 and 2 requires diligent attention to details: mechanical and chemical
- Dosage forms can respond differently to small variations in apparatus set up or degassing
- Large differences in dissolution results are possible unless all parameters are carefully controlled
- Differences in reproducibility can often be traced to improper mechanical calibration and/or degassing

Cindy Buhse
Director, Division of Pharmaceutical Analysis
FDA/CDER/OPS/OTR

Process Capability and Measurement Capability: Dissolution Test

- When we evaluate process capability by measuring variability in the product produced
- Total variability σ^2_{Total}
  - Assuming independent variable (if not independent for example interaction between measurement and product a covariance term needs to be included)
  - $\sigma^2_{Total} = \sigma^2_{Product} + \sigma^2_{Measurement}$
  - $\sigma^2_{Measurement} = \sigma^2_{Repeatability} + \sigma^2_{Reprodicibility}$

In an OOS Situation – the question is what went wrong?

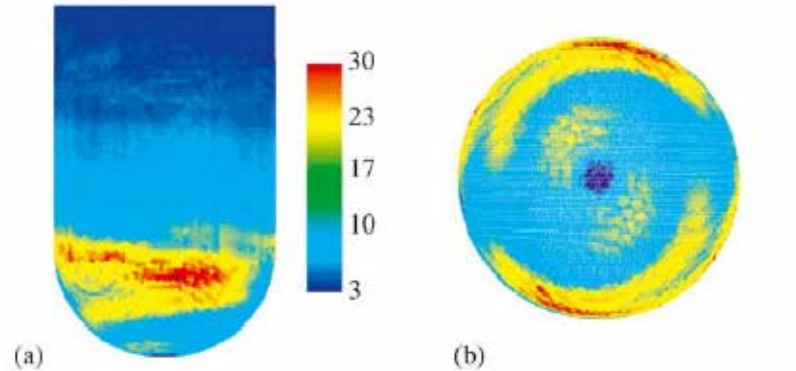
- Repeatability – inherent precision of the test procedure (did this change?)
- Reproducibility – different operator, different time period, different environment,… (is this a problem?)
- Destructive sample – what should we use to evaluate repeatability and reproducibility?
  - A USP Dissolution Calibrator Tablet?
  - Tablets from clinical batch?
    - Statistical approaches are available for ensuring appropriate sample of reference
  - Difficult questions; a need exists for further discussion on this topic

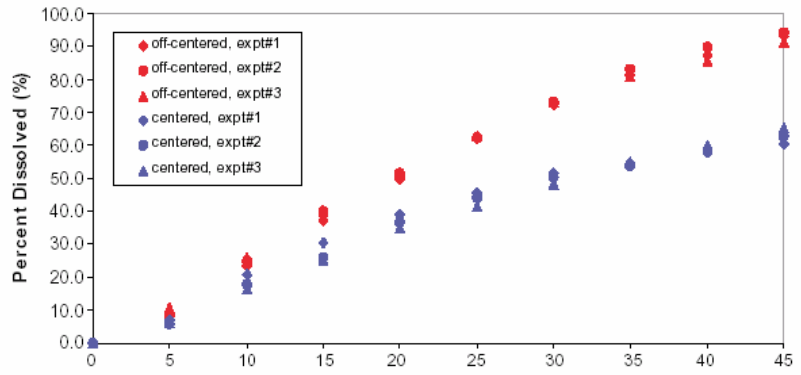
Difficult questions faced by Manufacturing Groups and Regulators…

- If we chose to use a calibrator tablet for a Gauge R&R study….
- $\sigma^2_{(\text{Total for Calib.})}$
  - $= \sigma^2_{(\text{Calib.})} + \sigma^2_{\text{C*Measurement}}$
  - What is the measurement for the Calibrator and what is its variability? $\sigma^2_{(\text{C*Measurement})}$
  - Since $\sigma^2_{(\text{Calib.})}$ is not known; we have to use $\sigma^2_{(\text{Total for Calib.})}$
- $\sigma^2_{\text{Total for Product}} = \sigma^2_{\text{Product}} + \sigma^2_{\text{Total for Calib.}}$

Difficult questions faced by Manufacturing Groups and Regulators…

- Assumption of independent variable?
- Another aspect – is the measurement capability for a Calibrator tablet representative of the drug product? What if there are differences such as disintegration mechanism and buoyancy between the Calibrator and the drug product?





J. Kukura, J.L. Baxter, F.J. Muzzio* International Journal of Pharmaceutics 279 (2004) 9–17

Options for reducing $\sigma^2_{Product}$?

- Given that there is an OOS situation, how can we reduce variability?
  - Reduce $\sigma^2_{Total\ for\ Calib.}$
    - Since acceptance limits for dissolution calibrator tablets are wide and improper mechanical calibration may not be detected
    - Modify set-up procedures (e.g., "degassing" protocol) or use "Sinkers" - How should these steps be justified?
    - If these steps do not do the job – then "it is what it is"
- By the time this is resolved several lots would probably have been rejected

Options for reducing $\sigma^2_{Product}$?

- Reduce $\sigma^2_{Product}$
  - Often during development the same or similar dissolution test method is used to generate the average "response" dissolution profiles for identifying and optimizing formulation and process conditions
    - Are any relevant information on "variability" available in the development reports?
- Caution: Observed variability in the production setting can be "common cause" variability and attempts to alter processing parameters without good information can create a bigger problem

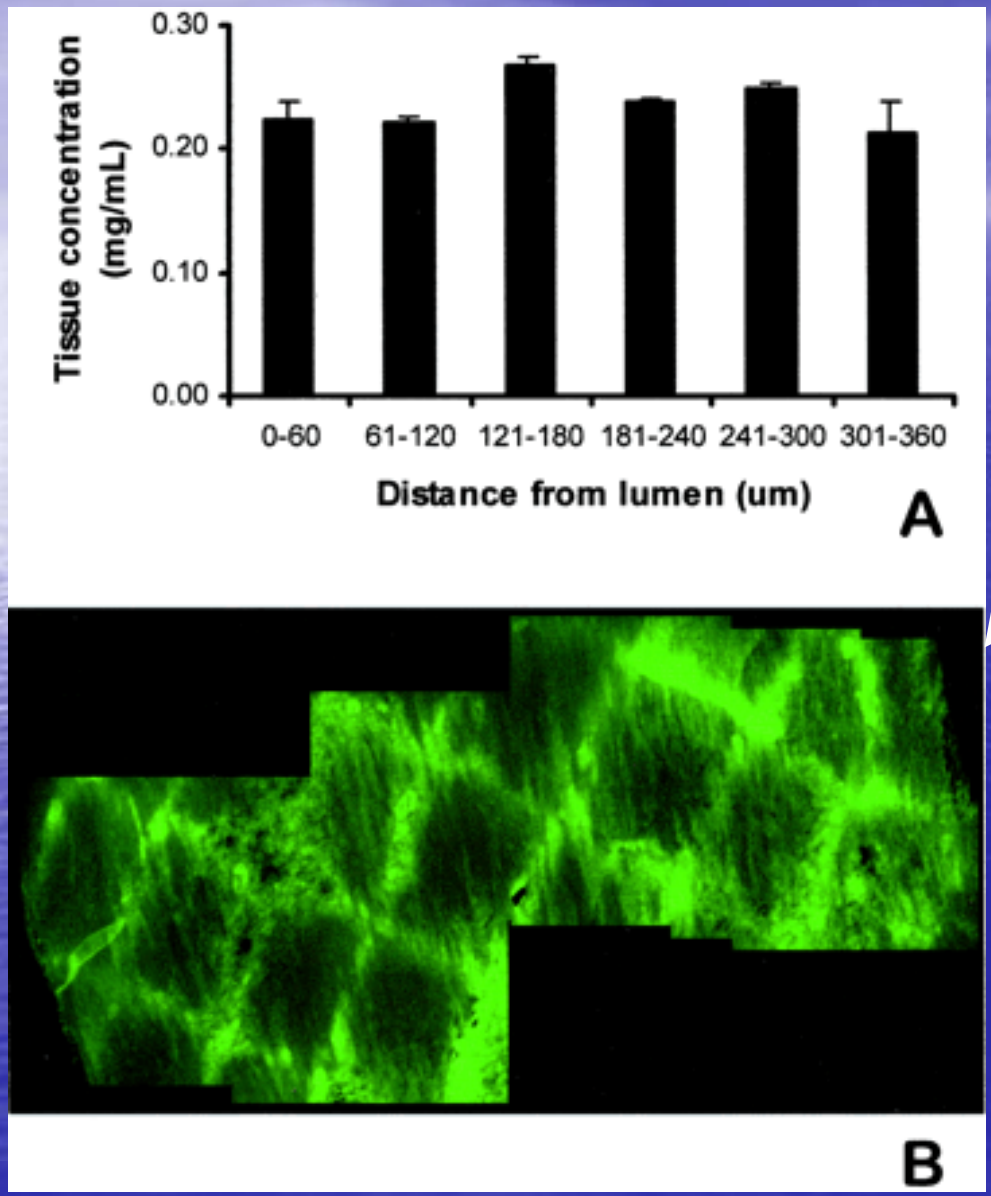
Difficult questions faced by Manufacturing Groups and Regulators…

- What is the capability of the manufacturing process used to make calibrator tablets?
- Can a company document improvement in a manufacturing process capability beyond that of the process used to manufacture the calibrated tablet?
    - How?

Characteristics of Stent-Based drug delivery (Circulation. 2001; 104:600-605)

- Tissue concentration variability
  - when we use conventional approaches (bulk elution) to simulate uniformity of drug targeting it yield a flat radial drug concentration profile (Figure A in the following slide)
  - A more detailed evaluation (using quantitative fluorescence microscopy) provides a dramatic spatial heterogeneity in tissue concentrations (see Figure B in the following slide)
  - Microscopic imaging of arteries reveals zones of high an low concentrations that identically followed stent geometry

(Circulation. 2001; 104:600-605)



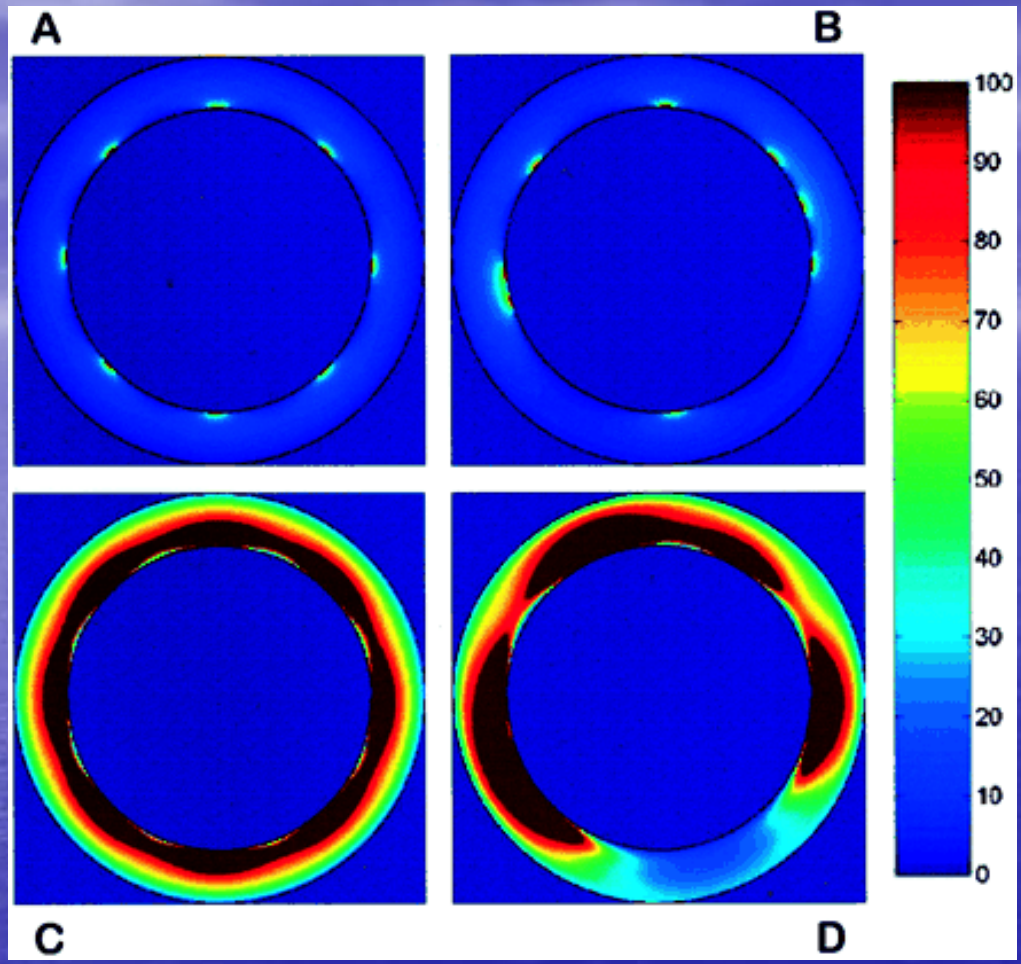
[A] Concentration profile obtained by bulk elution of serial en face sections.

Microscopic imaging of arteries reveals zones of high an low concentrations that identically followed stent geometry

[B] En face image of fluorescein distribution at 200 μm from luminal surface of bovine carotid artery

Models of Transport (Circulation. 2001; 104:600-605)

- Considerable variations of tissue drug concentration are present after stent delivery for both hydrophilic and hydrophobic drugs (see figure on the next slide)
- Large areas of high and low drug concentration exists simultaneously at steady sate
- Both circumferential and radial concentration gradients are greates near the struts and decay rapidly away before increasing again near the perivascualr space
- Although hydrophobic drugs manifest similar variation pattern to hydrophilic drug, they nevertheless distribute better



Large concentration variations resulting from stent-based drug delivery in a simulation modeling balanced convective and diffusive forces from 8-strut stents with homogeneous (A, hydrophilic; C, hydrophobic) and inhomogeneous (B, hydrophilic; D, hydrophobic) strut distributions. Scales are in $\%C_{sd}$.

(Circulation. 2001; 104:600-605)

In Vitro Elution?

- Traditional drug release testing may not relate to local tissue portioning of the drug from the stent
- Relevance of traditional pharmacokinetics approaches for establish IVIVC also needs to be examined; especially for hydrophobic drugs

Stent-based drug delivery & In Vitro Elution Test Methods?

- Need to approach this challenge from the perspective of "product/process design" and "mechanism of drug release"
  - Focus on "control" of critical variables
  - More effective use of engineering process design and control
  - New tools (for example chemical imaging) to focus on critical variables that relate to performance
- Better integration of product development with pre-clinical and clinical evaluation
  - Establishing biological relevance of product and process design and improving ability to predict performance
  - Quality by design

Future is upon us …

- Challenges, especially in the domain of physical performance are very significant
- We need to learn from our past experience and reevaluate assumptions we take for granted
- Developing "general" test methods for physical performance may not be the most productive path
- A more fundamental approach that utilizes quality by design principles is the way forward