Pharmaceutical Product Quality and Informatics

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Office of Generic Drugs Initiatives

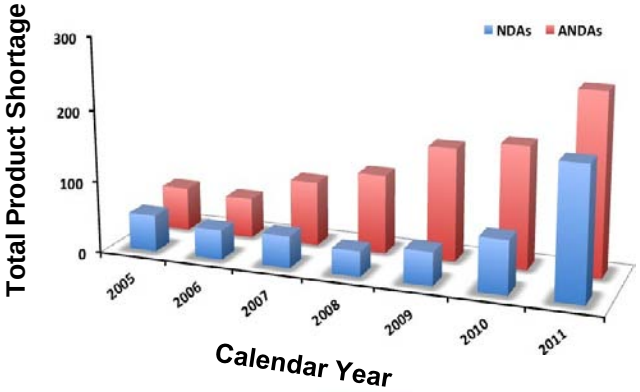
- Question-based Review
- Quality by Design for Generic Drugs
- Expertise-based Evaluation
  - Integrated Drug Substance and Drug Product Evaluation
  - Supplement Review
  - Peptide/Complex Drug Substance Review
  - Dosage Form Specific Review
- Risk-based Approach

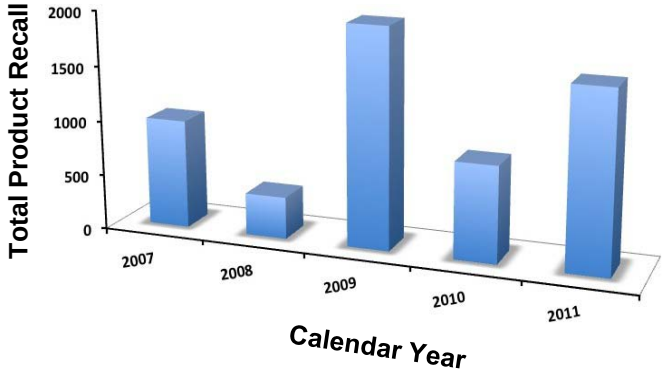
Vision

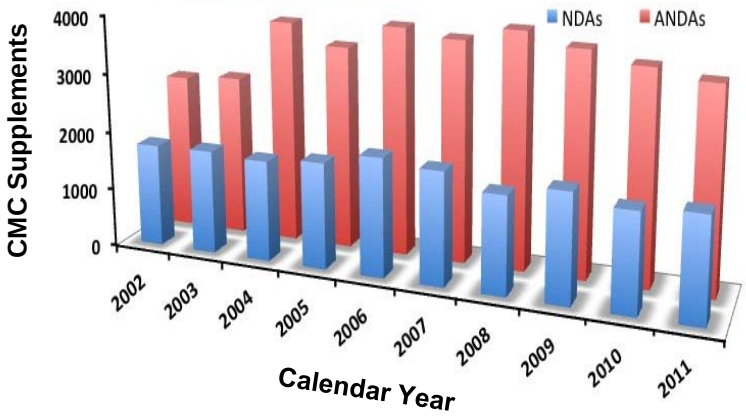
"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight"

Janet Woodcock, M.D.

We Aren't There Yet....







Why?

Industry
Regulatory
Academia

Industry

- Slow in developing and adopting new technology
  - Market place does not recognize value using new technology as all products approved by the FDA are created equal
- Industry implements the ICH continual improvement initiative unless there is a need

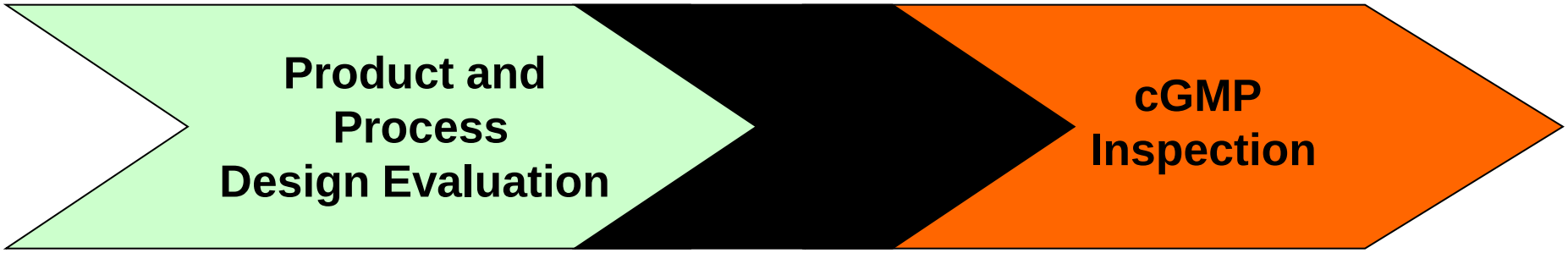
Academia

- Traditional industry pharmacy programs are shifting focus onto molecular biology
- The void is being filled by traditional engineering
  - This much needed research is encouraging
  - Continuous manufacturing process
    - It is highly likely that regulatory agency has to design a new process to deal with such advances

Regulatory

- Janet Woodcock
  - "Regulatory oversight one factor in lack of industry adoption of modern manufacturing technology"

Current Review and Inspection Model: Issues



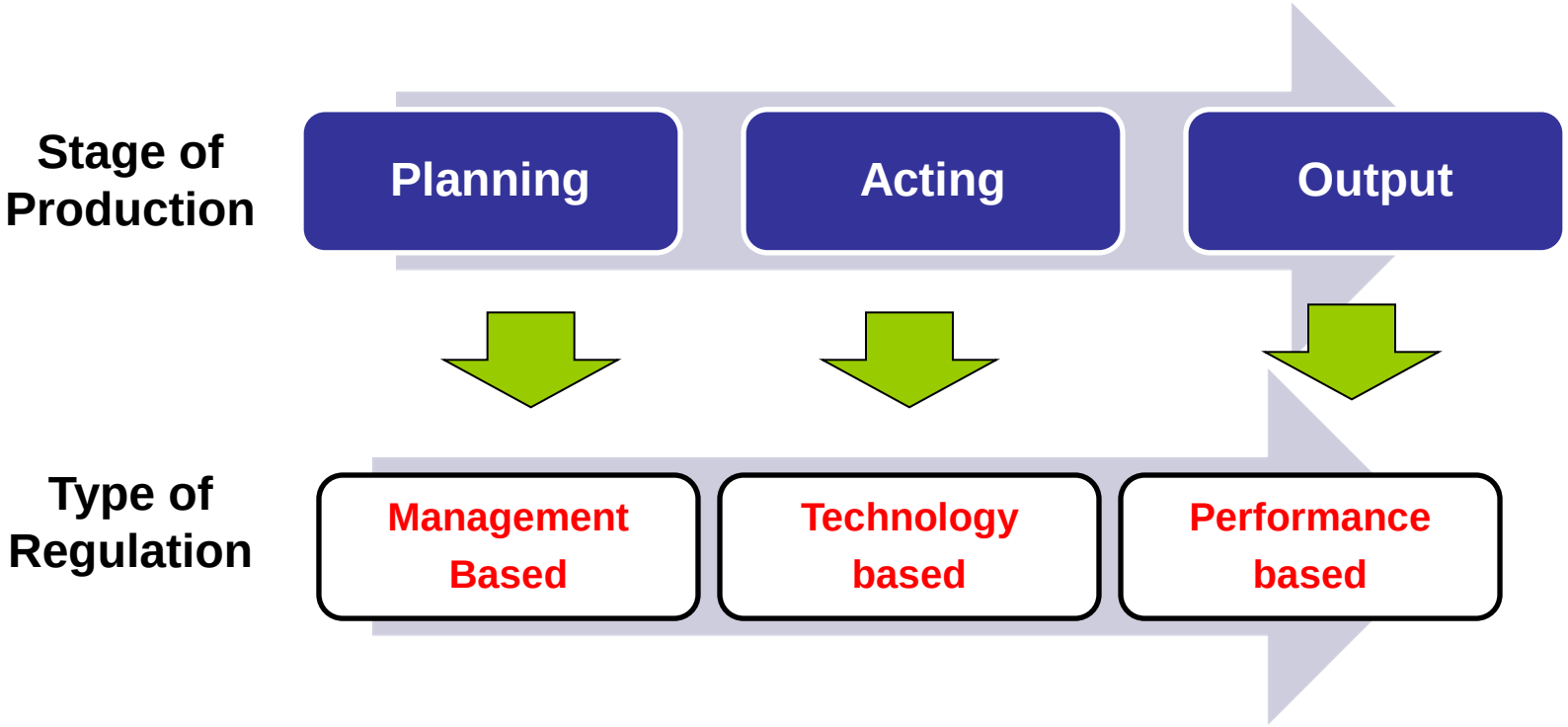
- **Extensive pre-marketing review**
- **Little flexibility**
- **Scale-up**
- **“Design space”**

Possible New Review, Surveillance, and Inspection Model

- **Integration of review and inspection**
- **State of inventory**
- **“Flexibility”**

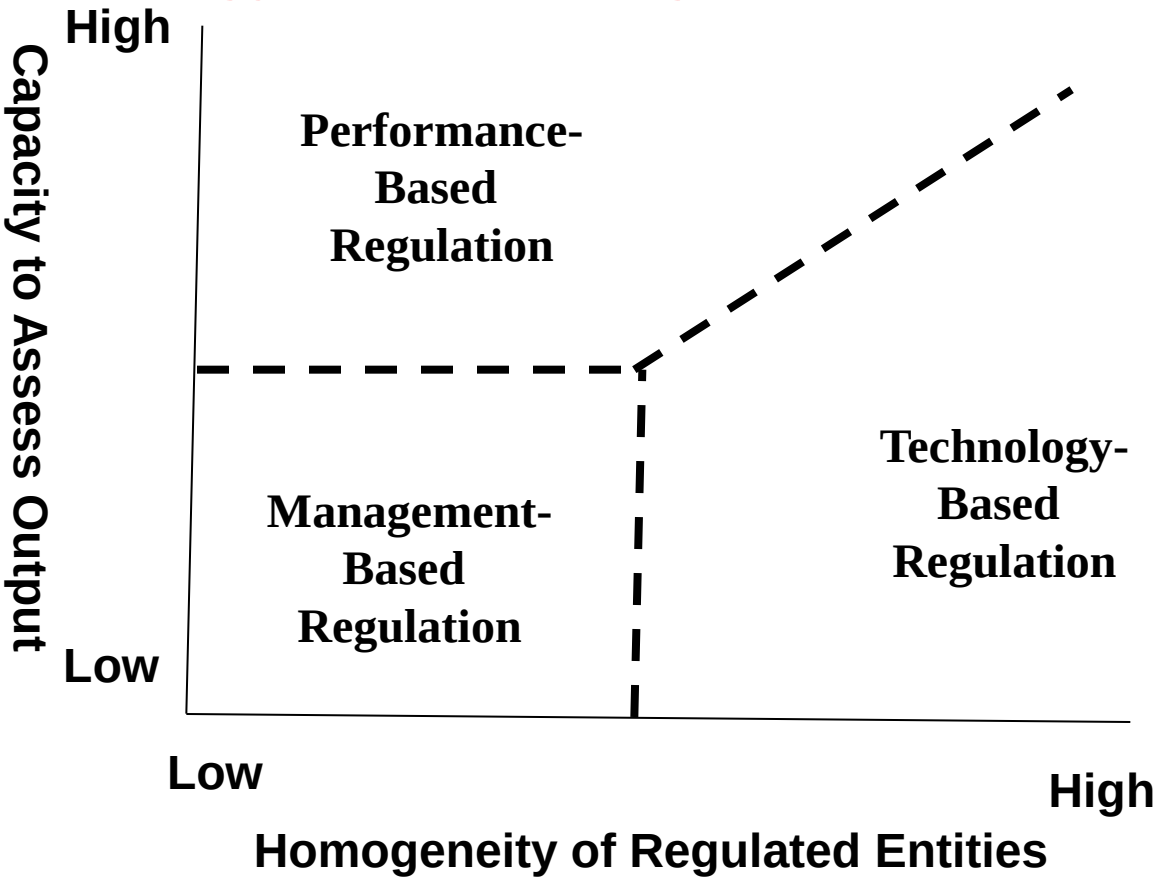
Regulation: Theoretical

Stage of Organizational Product and Types of Regulation



Coglianese, Cary and Lazer, David, "Management-based regulation: prescribing private management to achieve public goals" (2003). Computer and Information Science Faculty Publications. Paper 3. http://hdl.handle.net/2047/d20000315

Necessary Conditions for Effective Use of Performance, Technology, and Management Standards



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Process Capability

- Process capability (PC) is defined as the natural or undisturbed performance of a process after extraneous influences are eliminated
  - $\boldsymbol{PC = 6\,\sigma_{ST}}$
  - σ_{ST} is the inherent variability of a stable process
- Widely used by the other industries to measure and improve processes, its use in pharmaceutical industry is limited

Process Capability Index

Index	Description
$C_p = \frac{(USL - LSL)}{6\hat{\sigma}}$	Estimates process capability when the data mean is centered between upper and lower specification limits.
$C_{pkl} = \frac{(Mean - LSL)}{3\hat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of a lower limit only.
$C_{pku} = \frac{(USL - Mean)}{3\hat{\sigma}}$	Estimates process capability when the data mean is not centered between upper and lower specification limits or when specifications consist of an upper limit only.

USL = upper specification limit
LSL = lower specification limit

$\hat{\sigma}$ (sigma hat) = inherent variability due to common cause of a stable process

Process Performance Index

- Process performance is a statistical measure of the overall variability of a measured quality attribute from a process that may not have been demonstrated to be stable
- Pp, Ppk, Ppku, Ppkl…

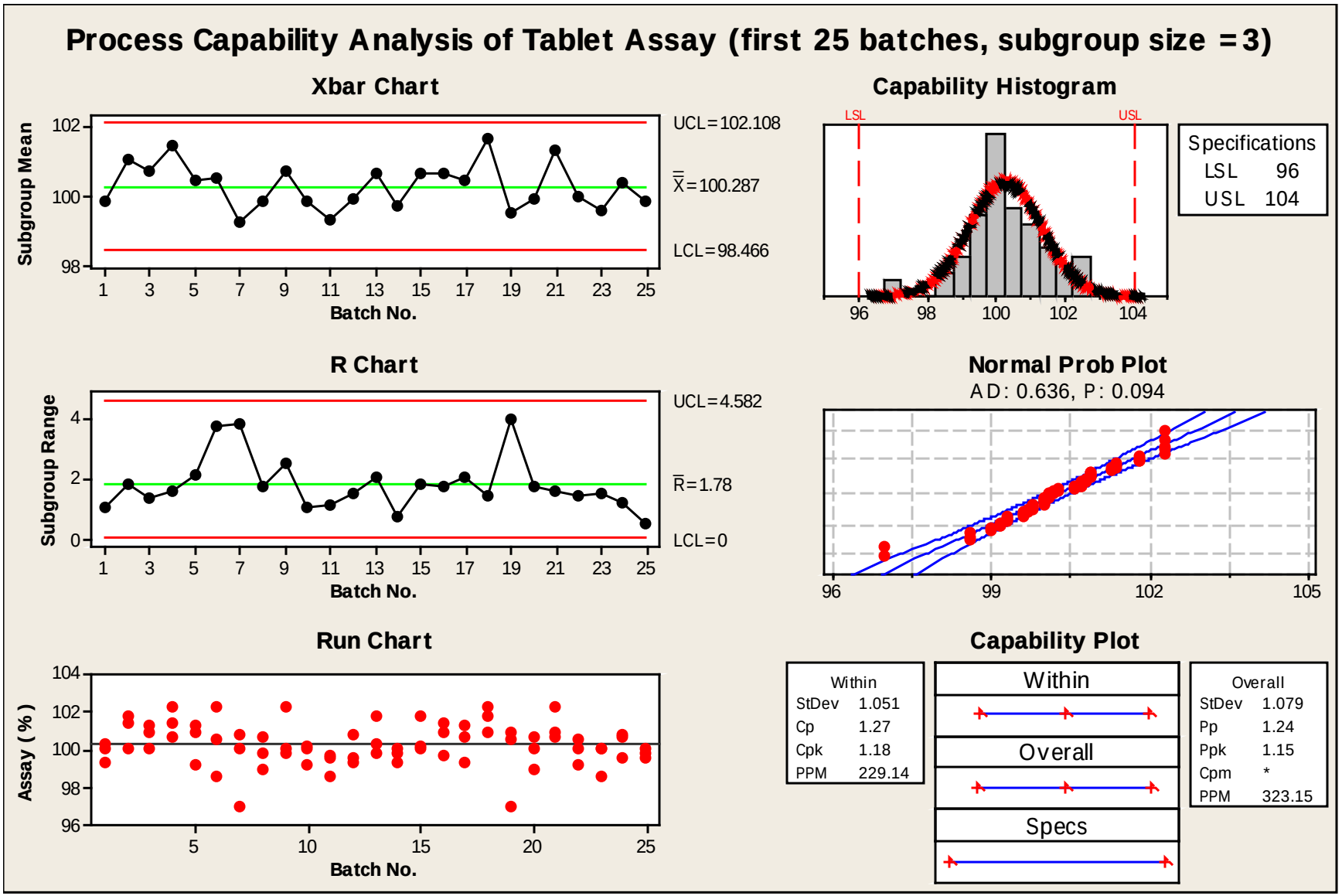
Control Chart

- Depending on the subgroup size, different types of control charts can be used to estimate process variability
  - When subgroup size is equal to one, individual chart (I-chart) and moving range chart (MR chart) are used
  - When subgroup size is between two and ten, average chart (X-bar chart) and range chart (R-chart) are used; and
  - When subgroup size is greater than ten, average (X-bar) chart and standard deviation chart (S- chart) are used

Cpk Values and its Corresponding Non-Conforming Parts Per Million

Cpk Value	Sigma Value	Area under normal distribution curve (% Conforming level*)	Non-conforming parts per million (ppm)		Capability Rating
			Unilateral Specification	Bilateral specification*	
0.333	1	68.27	158650	317300	Terrible
0.667	2	95.45	22750	45500	Poor
1.0	3	99.73	1350	2700	Marginally capable
1.333	4	99.9936	32	64	Capable
1.667	5	99.99994	0.3	0.6	Good
2.0	6	99.9999998	0.001	0.002	Excellent

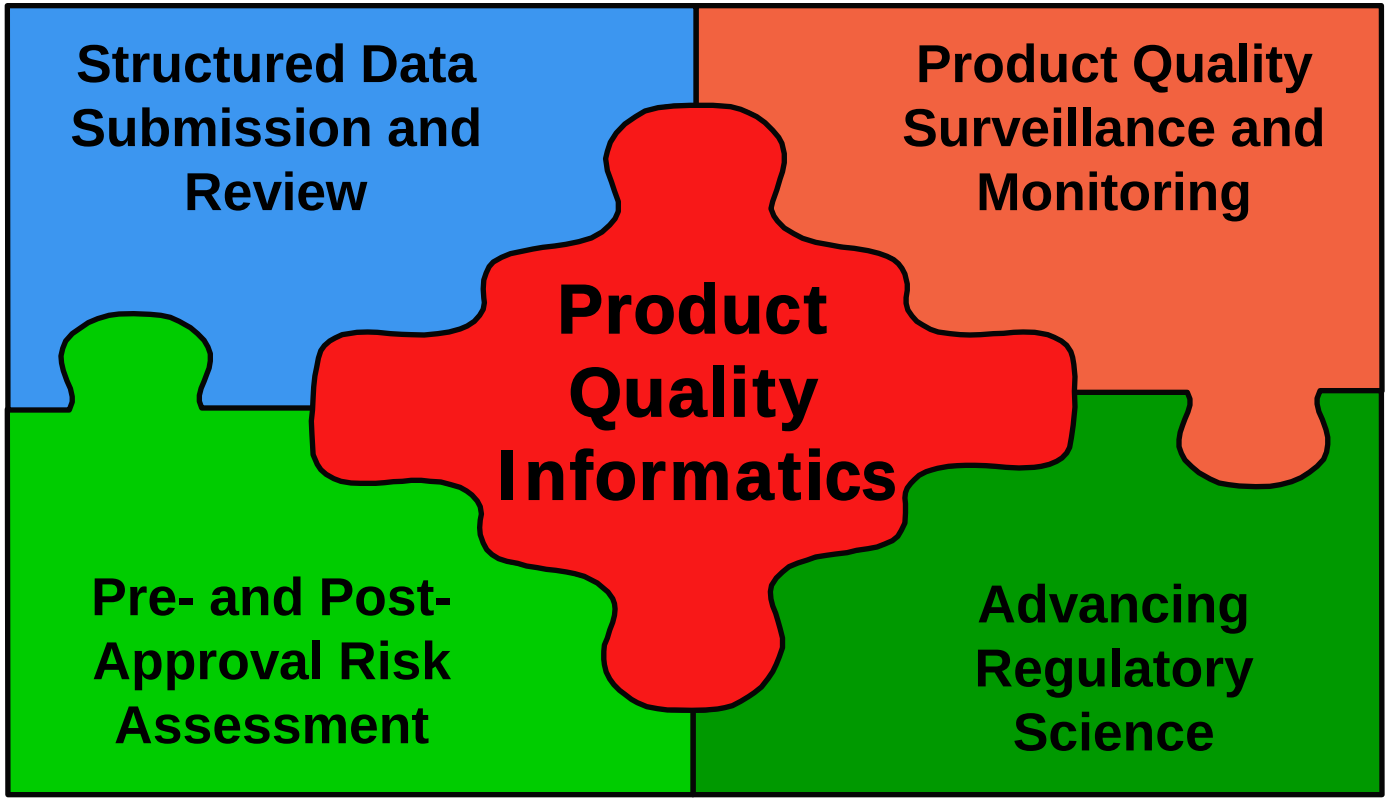
Process Capability: Example



Manufacturing Science and Predictability

- Strengthen systematic understanding of scale up for key pharmaceutical unit operations
- Computer-aided process modeling, simulation, and control
  - Widely used in other industries
  - Application in pharmaceutical industry is limited

Product Quality Informatics



Structured Data Submission and Review

- Data standards for submission and review of quality information need to be established in a harmonized way that facilitates the capture of quality information
  - drug substance physical, chemical, and biopharmaceutical property
  - drug substance synthesis and control
  - drug substance standard including analytical method
  - BCS classification (including solubility data)
  - therapeutic category

Structured Data Submission and Review (continued)

- dosage form and formulation composition
- pharmaceutical development information
- product manufacturing process and control
- container closure information
- product and excipient quality standard including analytical method
- Data on manufactured batches
  - Manufacturing site
  - Quality data including release and stability when appropriate

Product Quality Surveillance

- The hallmark of the quality surveillance is real-time compliance in which manufacturers provide electronic summaries of product quality to FDA
  - Continuous monitoring to identify trends that indicate problem within a product class and/or a manufacturer to reduce drug shortage
  - Particularly important as globalization
  - For-cause inspection

Advancing Regulatory Science

- Structured quality data will allow the evaluation of effect of excipients on manufacturability and performance
- Process modeling, simulation, and control
- Predictive models of process scale up
- Multivariate data analysis for characterization of complex drug substance and drug product
- Correlation of product quality with dissolution, bioavailability, and bioequivalence

- Product surveillance
- Optimization studies
- Continual improvement

- Robust QMS
- Quality metrics
- Surveillance model

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight"

- New quality and surveillance model: Process verification
- Timing of PAI

- Abbreviated review
- Reduced PAS
- Reduced PAI
- For cause inspection

- New quality oversight
- Performance standard
- Real time compliance
- Quality metrics