Case Studies - Engineering Quality in Pharmaceutical Product Development, Scale-up, and Process Validation

"Theory and Practice of Solid Oral Dosage Forms"

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Learning objectives & Framework

- Objectives:
  - Discuss how quality engineering has evolved
  - Review critical elements of QbD – current paradigms
  - Present systems approach for product quality & design QOD and QOC
    - DOE & Process Capability (C_{pk})
  - Discuss critical success factors
  - Provide adequate references

- Frame work:
  - Focus less on math
  - Focus more on philosophy, Approach
  - Provide case studies

Lecture Outline

1. Quality Modeling & Statistical Thinking
2. Quality by Design (QbD) – Key Elements
3. Quality of Design (QOD) & Quality of Conformance (QOC)
4. Optimization via DOE to establish QOD
5. Statistical Process Capability for QOC
6. Closing Remarks and References

Requirements & ASQ Definition

Voice of the Customer
•Regulatory Requirements
•Acceptable Quality Limits
(internal and external)

Voice of the Product / Process
•Process Capability
•Control Limits
•Product / Process Specifications

R&D, QA and Mfg Operations Satisfaction

Quality is Optimal Set of Characteristics at meet the voice of the customer (ASQ)

"Statistical Thinking" - Overview

- Summation of history of the problem solving, statistics and quality.
- Combine the best from many areas and fields into a coherent and internally consistent approach.
- Benefits include fewer out of spec results, reduced cycle time, faster and better validations, improved productivity and efficiency and better quality for consumer.

Statistical Thinking - Working Principles

- Philosophical and fundamental (ASQ statistical division)
  - All work occurs in a systems of interconnected processes.
  - Variation exists in all processes.
  - Understanding and reducing variation is key to success.

Statistical thinking - Concepts

- SIPOC model - global overview;
  - Supplier provides Inputs into Process activity; end result in Output that then goes into Consumer
- Processes can be mapped, flowcharted, studied systematically, understood and improved.
- Work is conducted by teams of people with differing backgrounds, education, expertise, skills, needs and expectations.
- Process outputs vary as a result of both systematic and random causes.
- Cause and effect relationships form foundation

  $Y = f(Xs)$…….

Statistical Thinking - Concepts (contd.)

- Variability is the enemy of cGMPS, validation, quality, productivity, efficiency, and profits.
- Variability can be measured, studied, and understood.
- Statistics is the science of variation.
- Variability in processes can be reduced. It is not fixed. Adopting a philosophy of running to target and working for consistency is needed.
- Organizations succeed by continuous improvement using teams to reduce variation and bring processes into statistical stability.

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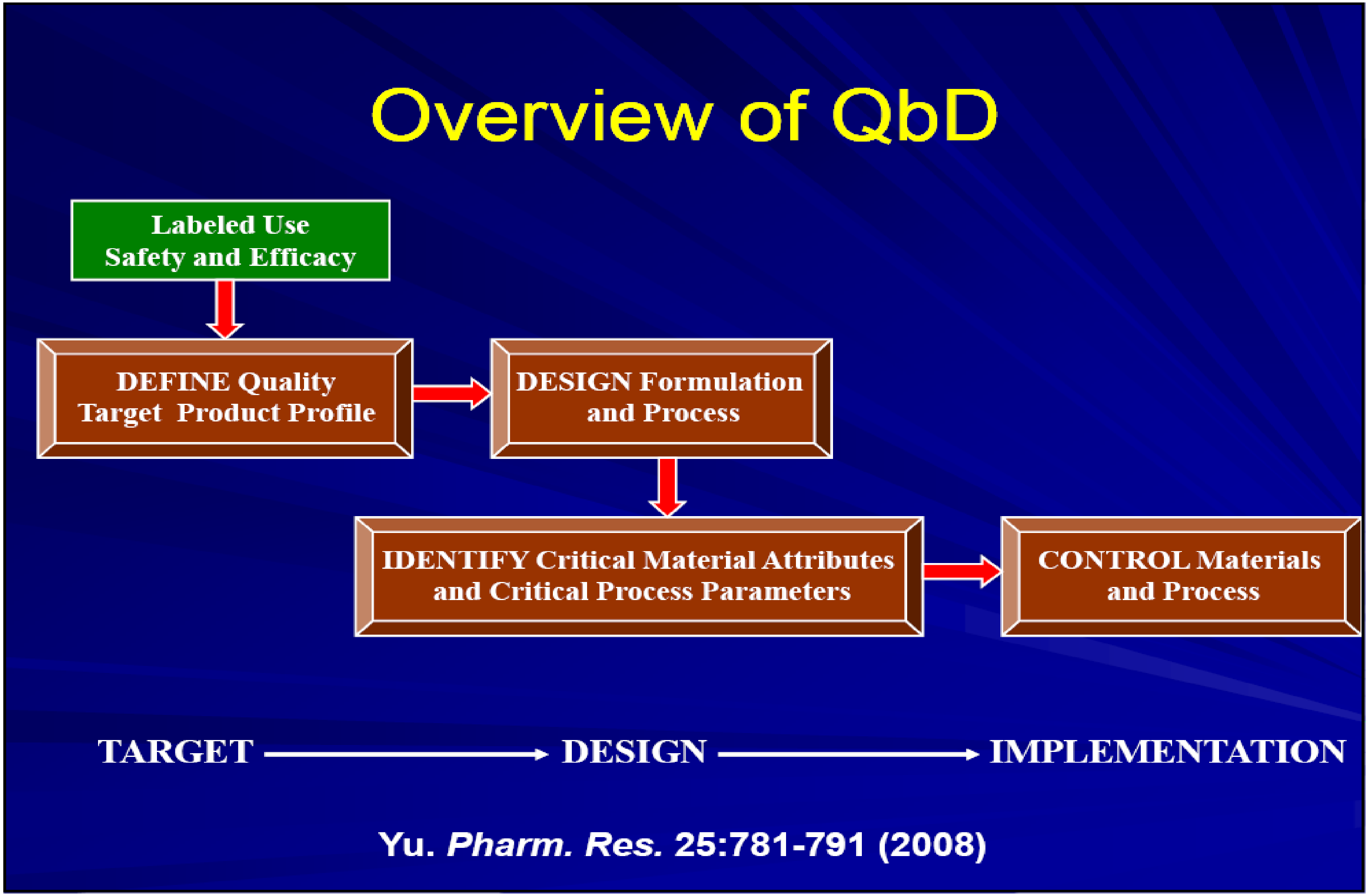
QbD Backdrop

- ICH Q8 (R2) Guidance Pharmaceutical Development – Current regulatory CMC paradigms

- Key premise:
  - Pharmaceutical QbD is a systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management
  - Quality cannot be tested into products; quality can only be built into products

General Schematics – FDA's Thinking



Simplified Quality Control Diagram using QbT

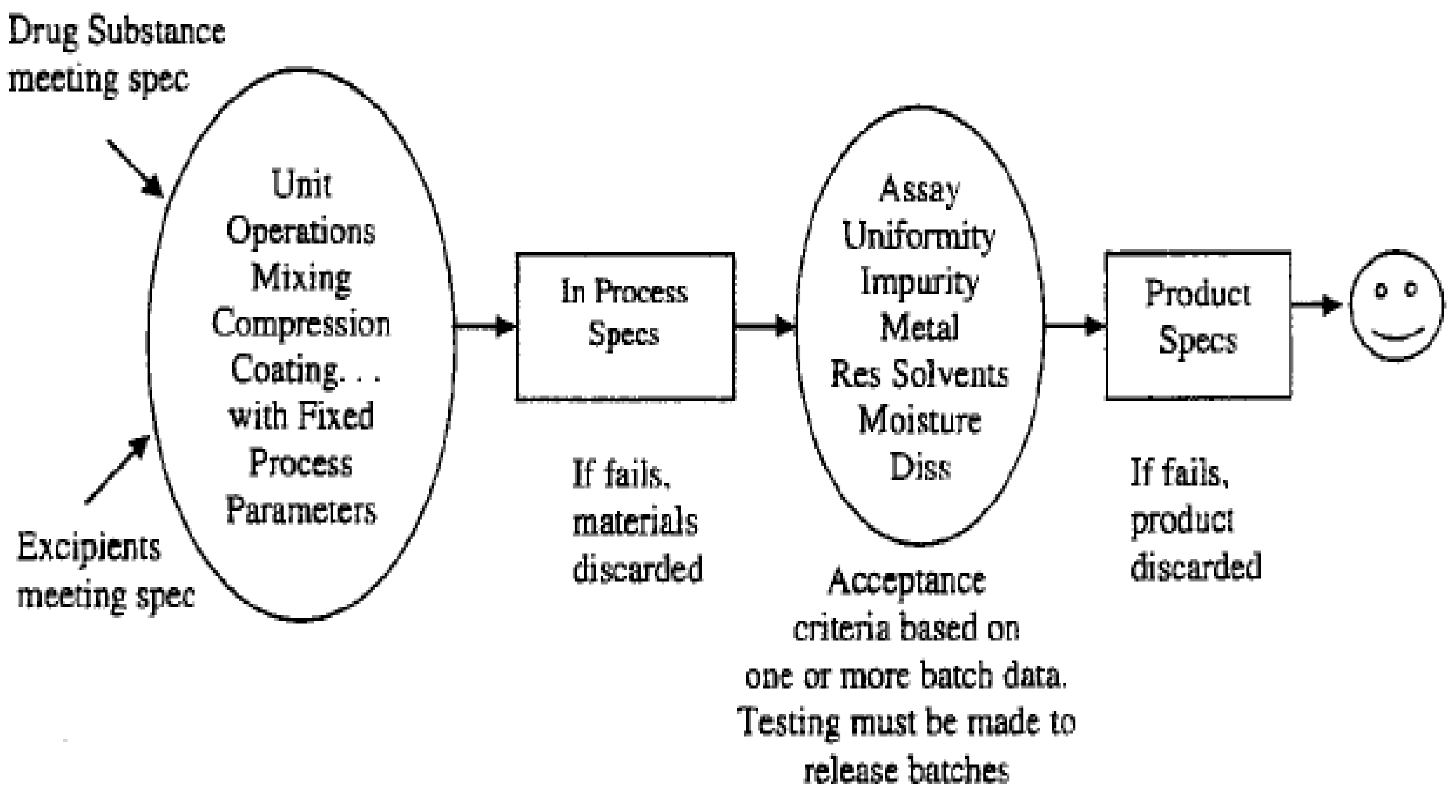
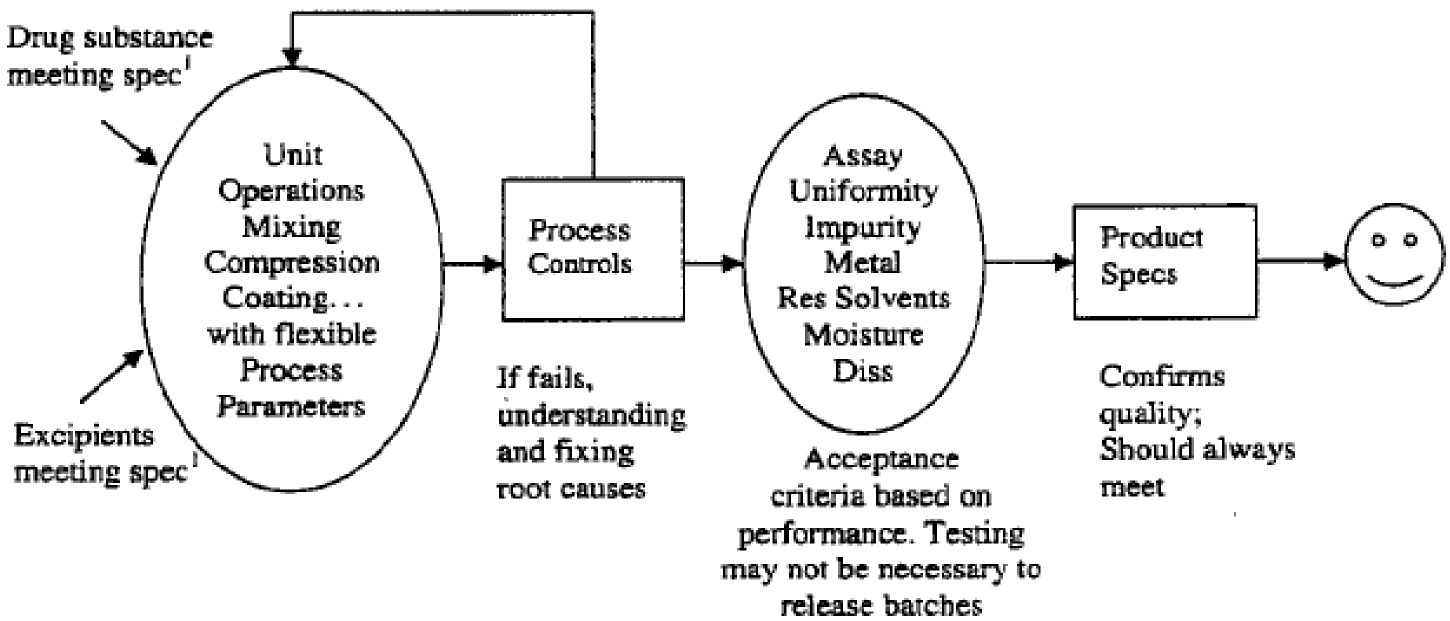


Fig. 1. A simplified quality control diagram using QbT.

Pharm Reserch, Vl 25, 4, April 2008, pg 781-791

Simplified Quality Assurance Diagram using QbD



Note:

[1]Drug substance and excipient specifications only contain critical attributes that will impact performance and processing of the product

Fig. 2. A simplified quality assurance diagram under the QbD for generic drugs.

Pharm Research, Vol 25, 4, April 2008, pg 781-791

Key Elements of QbD

- Define Quality Target Product Profile (QTPP)
- Design and develop product and manufacturing processes
- Establish design space
- Identify:
  - Critical Process Parameters (CPPs - Xs); Critical Quality Attributes (CQA –Ys); Sources of variability
- Compute Statistical Process Capability (C_{pk})

$$\text{Process capability index } (C_pK) = \frac{\text{Upper limit of specification} - \text{lower limit of specification}}{\text{6 standard deviation}}$$

- Control strategy to produce consistent quality over time

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Approach for QOD and QOC - Prior to QbD

Quality Engineering
Product Design & Conformance

Quality of Design (QOD)
- Product Suitability
- Product functionality
- Optimal Performance

Quality of Conformance (QOC)
- Product consistency
- Product Uniformity
- Product / Process Capability

Design Of Experiments (DOE)

Formulation and Process Development Phase

SPC & Statistical process Capability (C_{pk})

Process development, mfg phase III & ICH stability, scale-up and PV

1st Generation:
C_{pu}, $C_{p}l$, C_{p}, K, C_{pk}

2nd Generation:
C_{pm}, C_{pmk}

Robutst PCI: C_{Θ}

Quality of Design (QOD)

- QOD refers to product suitability (via DOE)
- QOD pertains to product functionality and its potential for achieving highest Quality of Conformance (QOC)
- QOD can be applied, to build quality, in:
  - Research: Identify key factors
  - Formulation: Optimizing formulation design
  - Process: Optimizing process design, evaluate robustness
  - Improvement: Trouble shooting experiments
- Understanding input-output relationships is key
- Knowledge of science and technology is prerequisite

Quality of Conformance (QOC)

- QOC refers to product consistency
- QOC pertains to uniformity of product attributes
- QOC can be applied in:
  - Process design: Establishing design criteria
  - Process control: Quantifying quality !
  - Sampling: Sampling plans, AQLs, OC curves
  - Product release: Testing, verification, audit, etc.

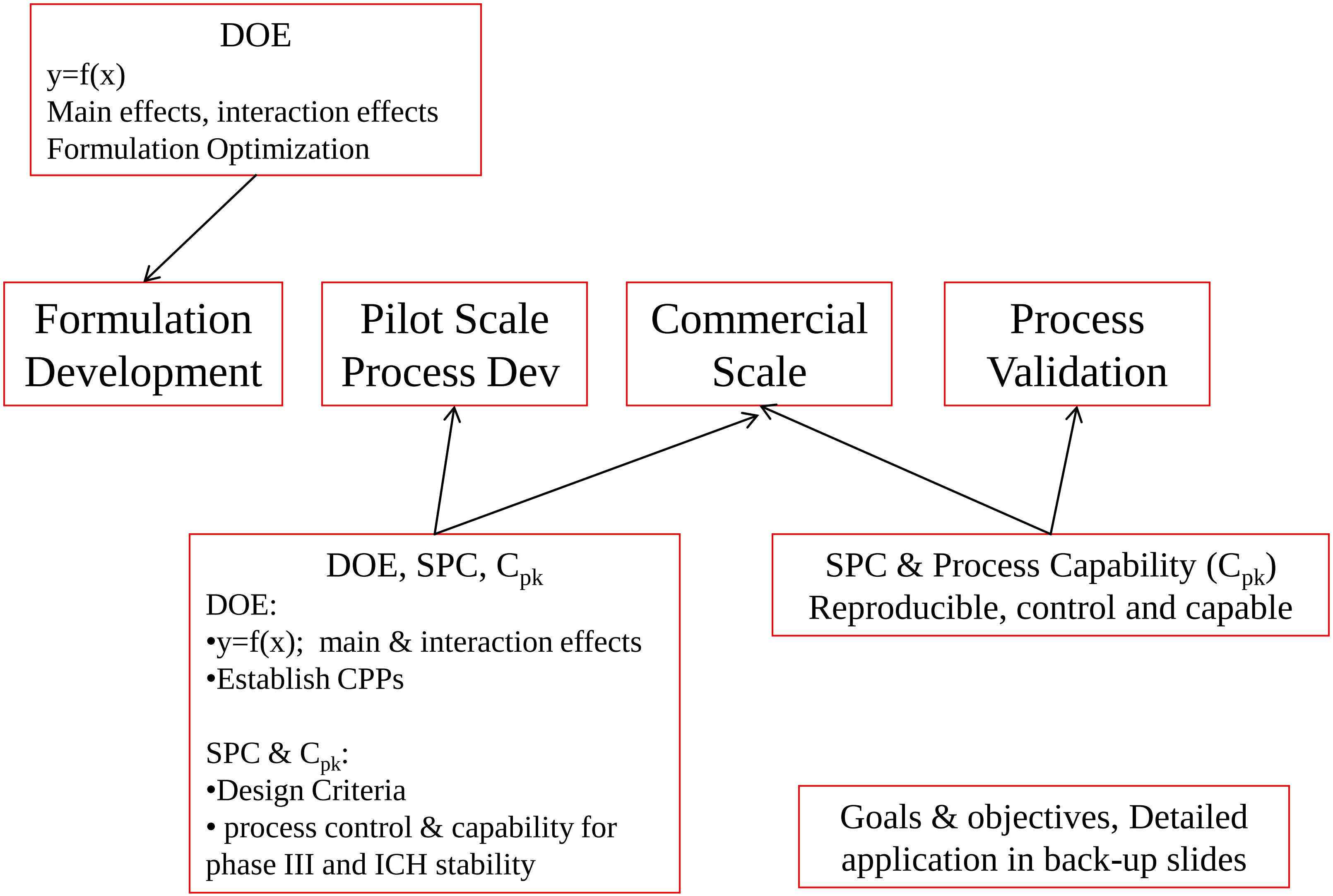
- Process Capability provides high degree of assurance for:
  - Process to conform to manufacturing limits
  - Product to conform to specification limits
  - Quantify process performance during process validation
  - Can form the basis for process validation

Systems Approach for QOD & QOC

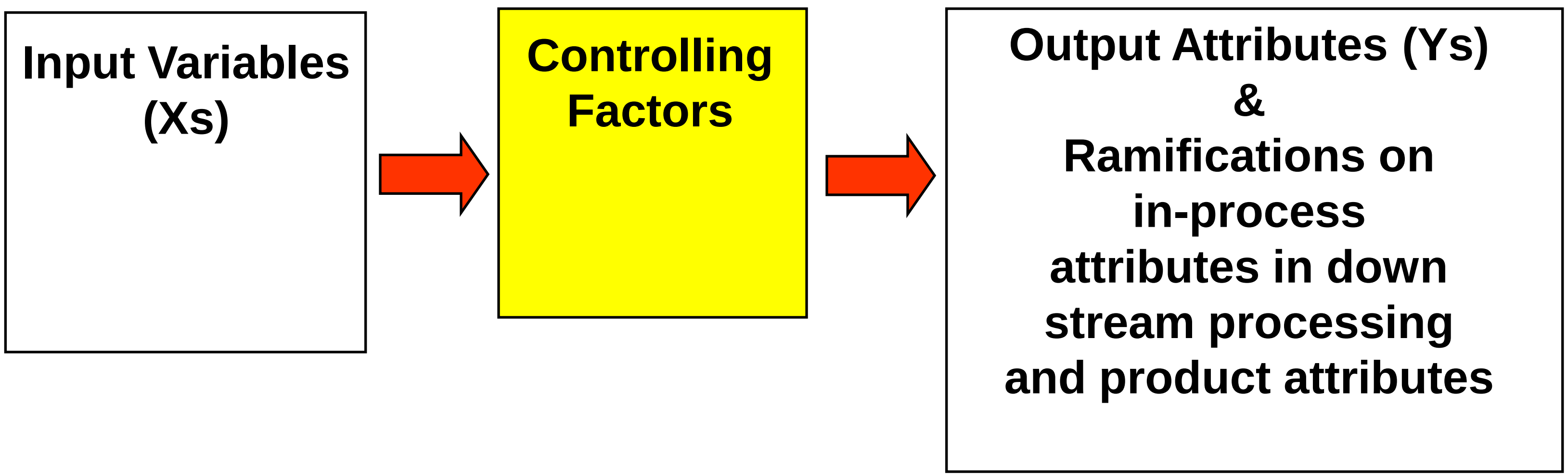
- Develop experimental strategies for effective PD programs

- Using systems approach, the development team can:
  - Achieve better product attributes
  - Decrease development time
  - Establish robustness
  - Enable high quality prediction
  - Engineer Quality
  - Quantify quality
  - Maximize benefit-cost ratio for experimental effort

Applying QOD & QOC in PD cycle



Systems Approach (I/O model)



Understanding the relationships between input variables and output variables is critical to process development & optimization

Fluid Bed Granulation Process (FBG)

Input Variables

1. **Thermodynamics:**

   Inlet Temperature, Air Volumes….

2. **Mist conditions:**

   Spray Rate, Atomization Air Pressure, Nozzle Size…

3. **FBG Equipment:**

   Filter bag size, Spray arm height, bottom mesh/plate….

Controlling Factors

Moisture Profile (LOD vs. Time)

During spray and drying cycles

Agglomeration

Output Variables

1. **Granulation Physicals:**

   Particle size analysis, bulk density, tap density, flow attributes, morphology, etc.

2. **Compressibility:**

   Compression force vs. hardness

Milling (Communition) Process

<u>Input Variables</u>

Screen Size, Speed, Mill Type, Knives/Impact

<u>Controlling Factors</u>

Fracture Mechanism, Shear

<u>Output Variables</u>

1. **General**

   Particle Size Distribution, Specific Surface Area, etc.

2. **Active Milling:**

   Dissolution profile

Blending Process

Input Variables

Speed (RPM), Time (minutes),

Fill (%)

Controlling Factors

Particle Movement

Output Variables

1. **General**

   Particle Size Distribution, Blend Uniformity, density, etc.

2. **Compressed Tablets:**

   Dissolution profile

Tablet Compression Process

Input Variables

Turret Speed, Compression Force, Diameter of Punch Head, Feeder mechanism, pre-compression, etc

Controlling Factors

Dwell Time, Residence Time, Porosity vs. Thickness (Heckle Plots)

Output Variables

1. **Tablet Physicals:**

   Weight, Hardness, Thickness

2. **Dissolution Profile**

3. **Compression Consistency (SPC and Process Capability)**

Tablet Film Coating Process

Input Variables

1. **Thermodynamics:** Inlet temperature, Air Volume
2. **Mist Conditions**: Spray Rate, Atomization Air pressure, Nozzle Size, Air Cap, etc.

Controlling Factors

mft > T_g

Outlet Temperature > mft

Rate of drying vs. Rate of spraying

Output Variables

Cosmetic/organoleptic

Coating elegance

Weight gain

Thickness increase

Surface Roughness

Disintegration Time

Functional coatings:

Dissolution Profile

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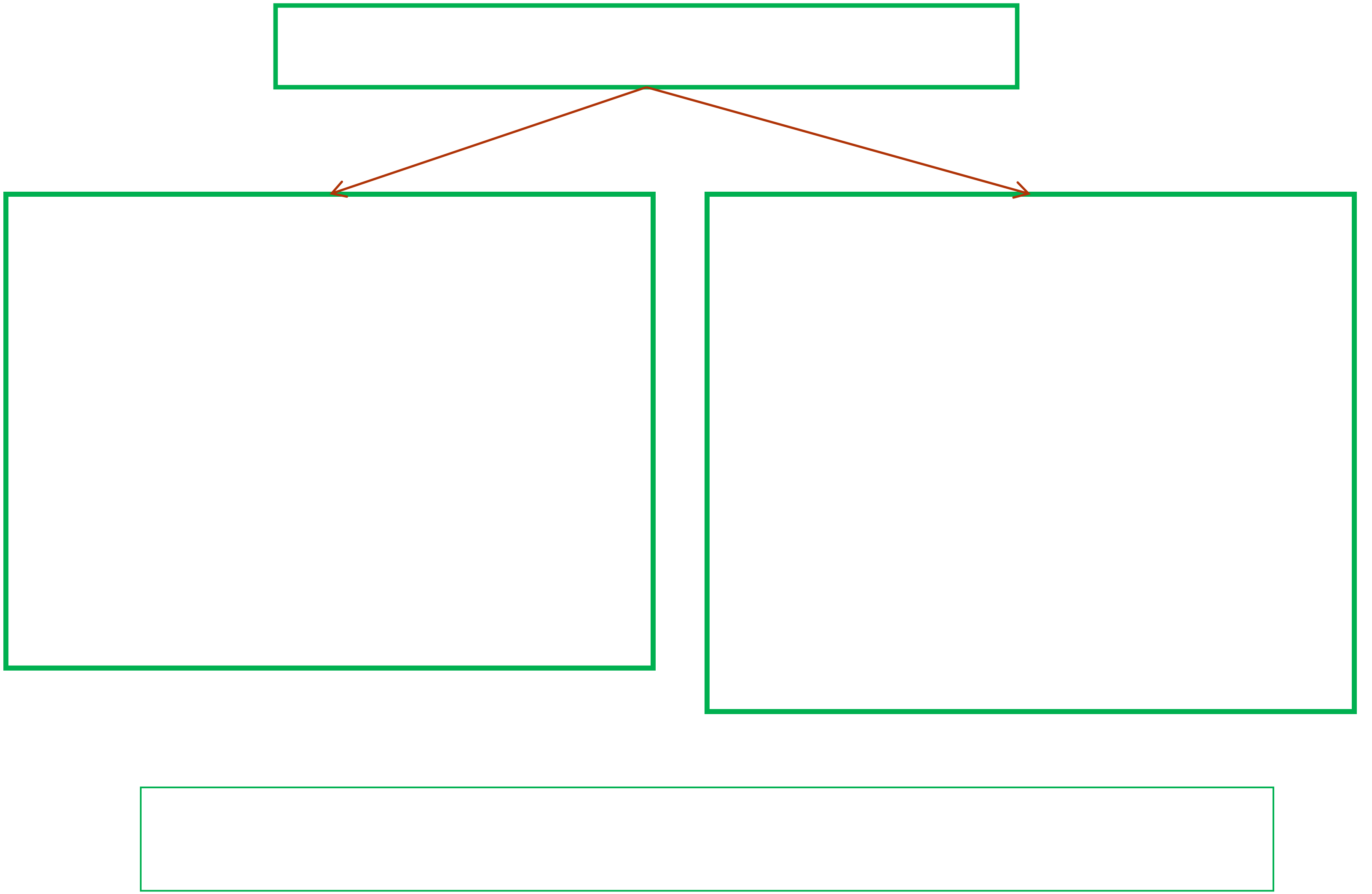
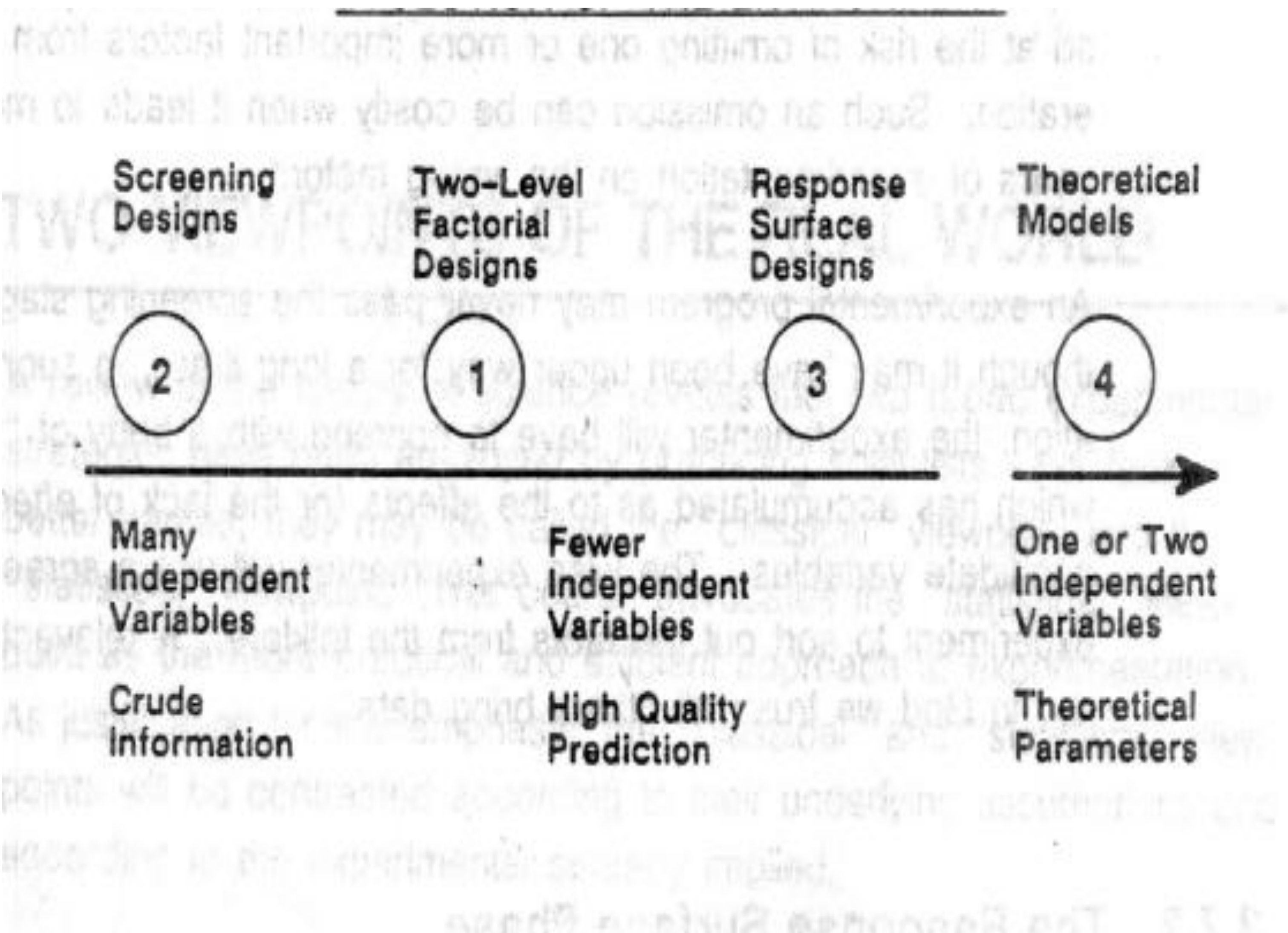


Evolution of Experimental environment



DuPont’s manuals on strategy of experimentation

General Evolution of DOE

Knowledge of science / engg experience, common sense

Identify Important Input Variables (Xs) and Properties / Out Put Variables (Ys)

Simplex Mixture Designs (Great for Formulation optimization, Mostly 3-4 factors - Xs)

Obtain

1. Y= f(x) and Optimize (maximize / minimize)
2. Can study main effects and interaction effects
3. Determine important Xs
4. Contour plots

Screening Designs (Plackett-Burman or Fractional factorial Great for formulation / process. Large number of Xs (> 8)

Obtain

1. Y= f(x); can maximize / minimize)
2. Can study main effects only; no interaction effects
3. Determine important X

Optimization designs – Box Benkhen, Full Factorial (Great for Formulation & process optimization, Mostly 3-4 key factors - Xs)

Obtain

1. Y= f(x) and Optimize (maximize / minimize)
2. Can study main effects and interaction effects
3. Determine important Xs
4. Response surface methodologies (RSM) / or

Case Study for QOD using DOE

- NDA Product, 10 mg/tablet

- Tablet Attributes:
  - Target weight: 150 mg, (142.5-157.5 mg)
  - Target Initial Hardness: 0.75 Kp, (0.50-1.00 Kp)
  - Thickness Range: 3.60-3.90
  - Shape & Size: 8mm, Round

- Objective: optimize treatment process and scale-up to commercial site

WOWTAB® - Formulation & Process

<Formula>

Mannitol	141.8
Maltose	7.5
Mg stearate	0.75
Total weight	150.0 mg

<Manufacturing flow>

Mannitol → Coating

Maltose, Water → Dissolving → Coating

Coating → Granulation → Mixing (+ Mg-st) → Tableting → Humidity treatment Drying

<Humidity treatment >

- Equipment

  Thermo-hygrostat

- Condition

  25^{o}C 70 %RH (24h) 30^{o}C 40 %RH (2h)

Case Study (contd)

Independent Variables	Levels	
Humidification Stage:	**Low (-)**	**High (-)**
X_1 – Humidity (%)	75	90
X_2 – Airflow (CFM)	75	125
X_3 – Time (min)	20	40
Drying Stage:		
X_4 – Temperature (°C)	30	50
X_5 – Humidity (%)	25	40
X_6 – Airflow (CFM)	75	125
X_7 – Time (min)	20	40

Dependent Variables
Y_1 – Final Hardness (Kp)
Y_2 – Final Moisture (%)

Fraction Factorial (2-level) Design

Run	X_1	X_2	X_3	X_4	X_5	X_6	X_7	Y_1	Y_2
1	75	75	20	30	25	75	20	4.82	0.266
2	90	75	20	30	40	75	40	5.70	0.751
3	75	125	20	30	40	125	20	4.21	0.763
4	90	125	20	30	25	125	40	5.20	0.603
5	75	75	40	30	40	125	40	4.19	0.923
6	90	75	40	30	25	125	20	5.36	0.807
7	75	125	40	30	25	75	40	4.48	0.752
8	90	125	40	30	40	75	20	5.57	0.898
9	75	75	20	50	25	125	40	3.16	0.383
10	90	75	20	50	40	125	20	4.84	0.533
11	75	125	20	50	25	75	20	3.63	0.787
12	90	125	20	50	25	75	20	4.60	0.520
13	75	75	40	50	40	75	20	3.75	0.676
14	90	75	40	50	25	75	40	4.58	0.313
15	75	125	40	50	25	125	20	3.16	0.967
16	90	125	40	50	40	125	40	4.01	0.478

Observed vs Predicted Values for Hardness

Run	Observed	Predicted	Residuals
1	4.82	4.81	0.01
2	5.70	5.77	-0.07
3	4.21	4.31	-0.10
4	5.20	5.13	0.07
5	4.19	4.20	-0.01
6	5.36	5.36	0.00
7	4.48	4.32	-0.16
8	5.57	5.61	0.04
9	3.16	3.29	0.13
10	4.84	4.59	0.25
11	3.63	3.54	0.09
12	4.60	4.70	-0.10
13	3.75	3.77	-0.02
14	4.58	4.59	-0.01
15	3.16	3.14	0.02
16	4.01	4.09	-0.08

Polynomial equation for final hardness (Y_1)

$$Y_1 = 4.5 + 0.53X_1 - 0.10X_2 - 0.07X_3 - 0.49X_4 + 0.03X_5 - 0.19X_6 - 0.09X_7$$

$R^2 = 0.98$

Optimal Conditions:

Parameter	Optimal Condition
Humdification Stage:	
X_1 - Humidity (% RH)	90
X_2 - Air Flow (CFM)	98
X_3 - Time (min)	28
Drying Stage:	
X_4 - Temperature (°C)	30
X_5 - Humidity (%)	35
X_6 - Air Flow (CFM)	94
X_7 - Time (min)	30

Optimization confirmation

Trial	**Final Hardness (Y1)**		
	Predicted	**Observed**	**Residual**
Trial # 1	**5.54**	**5.60**	**-0.06**
Trial # 2	**5.54**	**5.39**	**0.15**
Trial # 3	**5.54**	**5.30**	**0.24**

Scale-up to Commercial Site

- Pilot Scale (5Kg) to Commercial Scale (120 Kg)
- Only Air Volumes & Process Times to change
- Air Volume Calculation: $cfm_p \times (D_c/2)^2 / (D_p/2)^2$
  - Phase I: $98 \times (40/2)^2 / (13.75/2)^2 = 829$ cfm
  - Phase II: $94 \times (40/2)^2 / (13.75/2)^2 = 795$ cfm
- Process Time: $(cfm \times time/kg)_p \times (BS\ kg/cfm)_c$
  - Phase I :(98 cfm x 28min / 5 Kg) x120 Kg/829 cfm = 80 min
  - Phase II:(94 cfm x 30min / 5 Kg) x120 Kg/795 cfm = 85 min
- Hardness at Commercial Scale:
  - Batch1: 6.1 ± 0.22; Batch2: 5.9 ± 0.23; Batch3: 6.0 ± 0.13 (sample size: 150 tablets/batch)

Conclusions

- Tablet treatment process was optimized utilizing the DOE approach.
- The optimized treatment process upon scale-up to commercial scale & site resulted in hardness similar to R&D scale.

5. Statistical Process Capability

- Historical Perspectives
- Why ??? !!!!
- Assumptions
- Terminologies, computational methods
- Interpretation and Usage
- Broad Applications

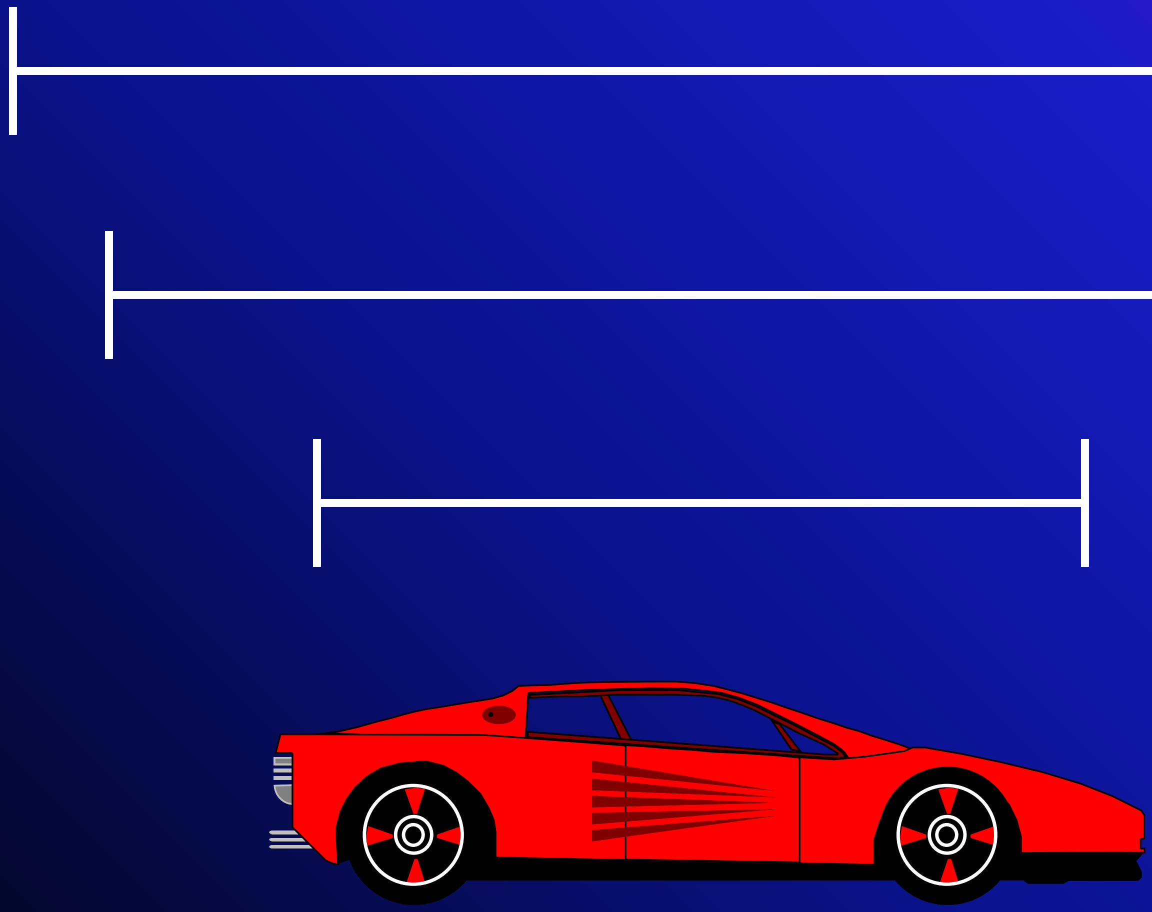
Historical Perspectives (SPC and Process Capability)

- Statistical process control (Schewart)
- Japanese Industry – Deming / Tagunchi…
- Motorola: 1983 National Quality Award
- Ford Motor Company, 1986
- Pharmaceutical literature, applications…

Why Process Capability?

- Provides a means for common and easily understood language for quantifying the performance of manufacturing process.
- Quantification of process location (mean) and variation (standard deviation) is central to product quality.
- Process capability provides a means to compute unitless indices (PCIs) using process location and variation relative to pre-established specifications (target & limits).
- Provides a measure for "High Degree of Assurance," a key requirement for process validation.

Parking Space



Assumptions

- The process is in a state of statistical control.
- The data are normally distributed.
- The data collected are collected from independent random samples.
- The data are truly representative of the process.

Summary of PCIs – 1st Generation

Index	Term	Equation	Usage
C_p	*Potential Capability*	$\frac{USL - LSL}{6\sigma}$	process potential for two-sided specification limits
C_{PU}	*Upper Capability Index*	$\frac{USL - \mu}{3\sigma}$	process performance relative to upper specification limit
C_{PL}	*Lower Capability Index*	$\frac{\mu - LSL}{3\sigma}$	process performance relative to lower specification limit
K	*Non-centering Correction*	$\frac{2 \mid m - \mu \mid}{USL - LSL}$	deviation of process mean from midpoint (m) of specification limits
C_{pk}	*Demonstrated Excellence*	$Min \{ C_{PL}, C_{PU} \}$ $= C_p(1 - k)$	process performance for two-sided specification limits

Interpretation

Approximately Normal	Exact Normal
$\mu \pm \sigma$ contains approximately 68% of the measurements.	68.26%
$\mu \pm 2\sigma$ contains approximately 95% of the measurements.	95.44%
$\mu \pm 3\sigma$ contains almost all of the measurements.	99.73%

Potential Capability - C_p (V. Kane); Using a $\pm$ 3σ spread, for a process with normal distribution:

C_p=1.0 means 0.27% of parts are beyond specification limits.
C_p=1.33 means 0.007% of parts are beyond specification limits.

To consistently achieve a C_{pk} of 1.33 during routine production, C_{pk} > 1.33 should be obtained in validation.

Broad Applications of Process Capability

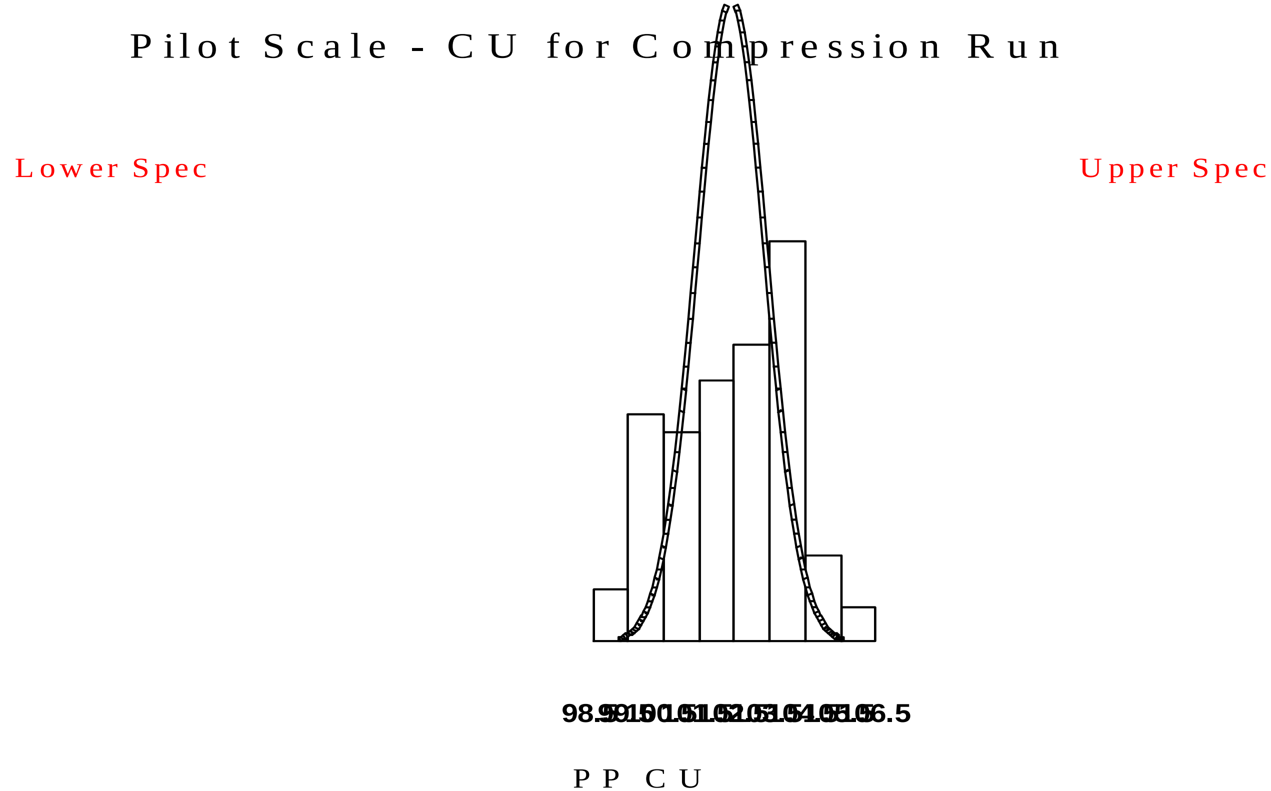
- Process Validation
  - Provides "high degree of assurance" !; C_{pk} is one way to quantify
- Design criteria during process development
  - 85-115 % CU limits
    - For Cp > 1.33; RSD < 3.75%
  - 90-110 % BU limits
    - For Cp > 1.33; RSD < 2.50 %
- Process performance quantification & predictability
- Generate rationale & establish in-process controls and specifications.
- Effect of process improvements

Case Study
Quantify process performance in PD cycle

- NDA Product; B.S: 15.0 Kg & 120 kg.
- Drug Loading: 6.7%; Compression Stage.
- Pilot: 3 batches; 5 samples; 6T/sample (n=90)

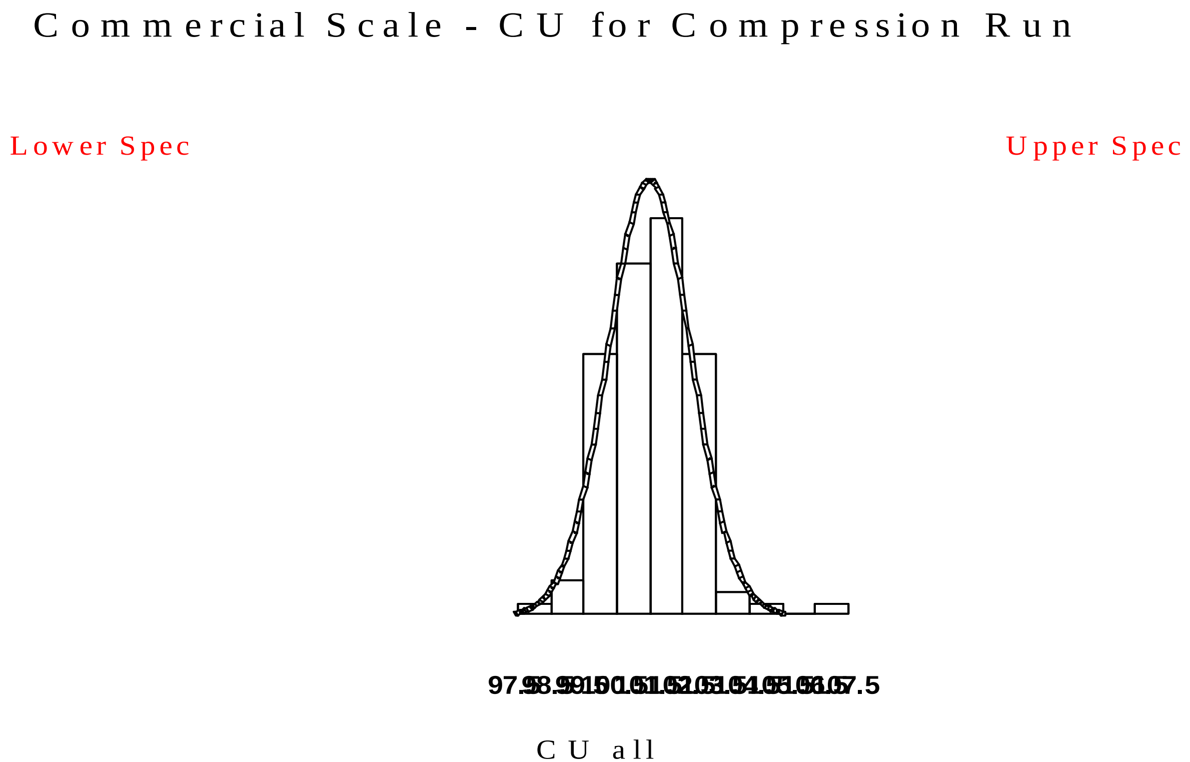
  Commercial: 4 batches; 10 spls; 3T/spl (n=120).
- Apply Process Capability for 85-115 % CU limits for pilot scale & commercial scales.

Process Capability - Pilot Scale



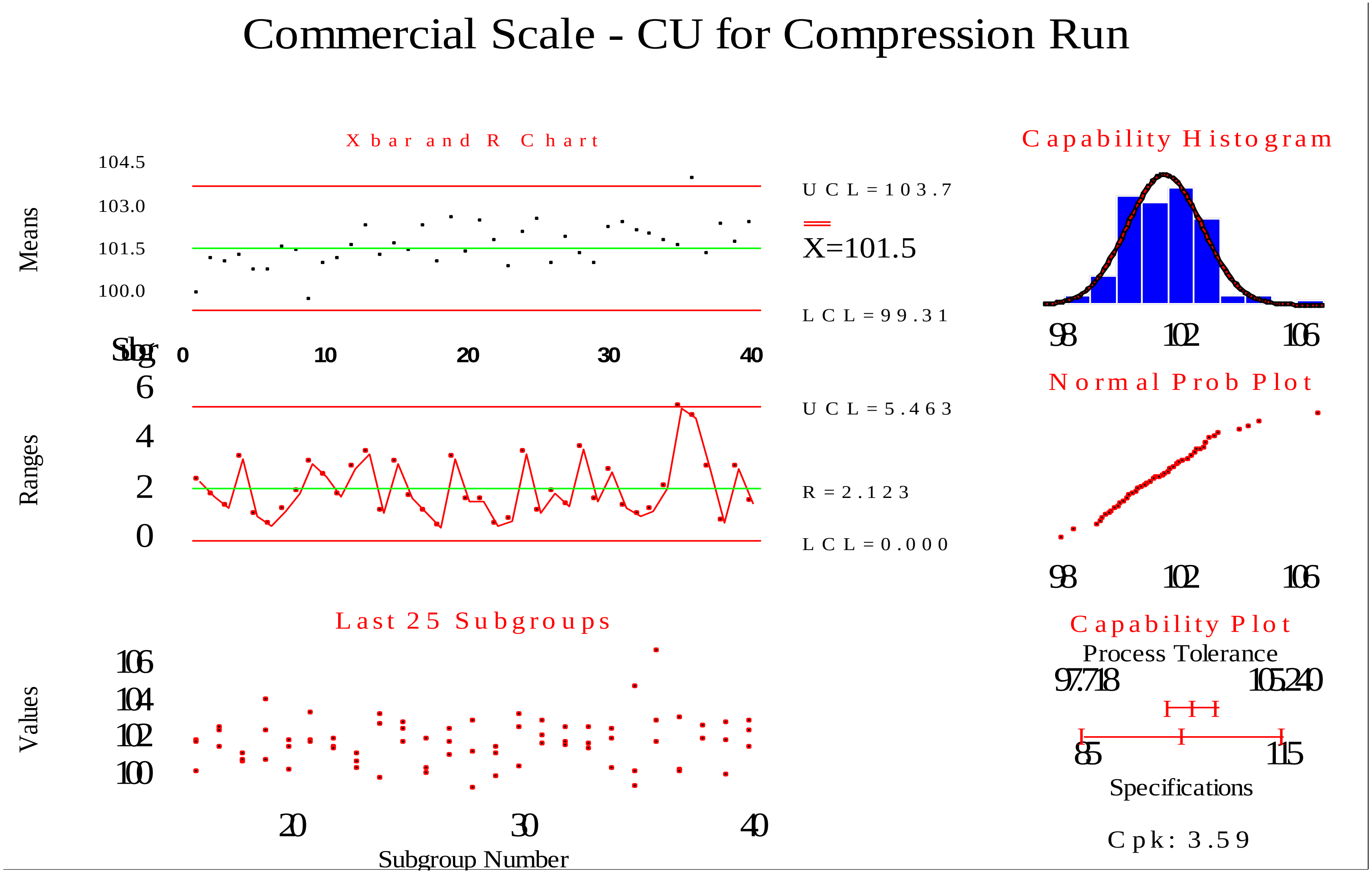
Cp	5.11	Targ	100.000	Mean	102.393	%>USL Exp	0.00	PPM>USL Exp	0
CPU	4.30	USL	115.000	Mean+3s	105.327	Obs	0.00	Obs	0
CPL	5.93	LSL	85.000	Mean-3s	99.459	%<LSL Exp	0.00	PPM<LSL Exp	0
Cpk	4.30	k	0.160	s	0.978	Obs	0.00	Obs	0
Cpm	1.68	n	90.000						

Process Capability - Commercial Scale



Cp	3.99	Targ	100.000	Mean	101.479	%>USL Exp	0.00	PPM>USL Exp	0
CPU	3.59	USL	115.000	Mean+3s	105.240	Obs	0.00	Obs	0
CPL	4.38	LSL	85.000	Mean-3s	97.718	%<LSL Exp	0.00	PPM<LSL Exp	0
Cpk	3.59	k	0.099	s	1.254	Obs	0.00	Obs	0
Cpm	2.55	n	120.000						

MINITAB Six Pack- Commercial Scale



6. Closing Reamrks
Compare QbD vs. Historical Quality Engineering

Parameter	QbD	QOD & QOC	Comments
Target Product Profile (TPP)	Key Element	Yes in terms of design objectives	Always a cross functional collaborative target
Design Space	Yes, an expected outcome of DOE	Result of DOE	suitable DOE strategy depends on needs
Critical Process Parameters (CPPs)	Yes	Expected outcome of DOE via main effects	Don't loose track of science and engineering
Critical Quality Attributes (CQA)	Yes	-	Listed in product specifications – those that effect SISPQ
Process Capability (C_{pk})	Yes	Yes and lot more	Relatively easy once you digest

QbD has put every thing in one place; look into variability from excipients, scalable across organizations, and has become norm rather than exception

Drivers to Product Quality

References – QbD, DOE, Process Capability

- QbD:
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Back-up Slides

Process Optimization Phase (Pilot Scale Stage)

Goals & Objectives:

- Establish a baseline manufacturing process that would render itself for commercial scale-up.
- Identify critical process parameters (targets and ranges) for all processing stages.
- Establish process robustness.
- Establish a basis for further, scale-up and manufacturing technology transfer to commercial scale and site.

Pilot Scale Stage

Application of Quality of Design (QOD)

- To Understand input-output relationships – empirically, statistically, worst case situations, common sense, etc.

- To Apply statistical DOE in order to:

  - Develop statistical relationships between independent variables (Xs) and independent/response variables (Ys) that would render high quality predictive power.

  - Identify set of experimental conditions/settings (for independent variables) that would result in optimal (maximum or minimum) value for key independent/response variable.

- To Ensure process integrity via extensive sampling and testing (physical and chemical) – extensive characterization of various in-process and finished product samples.

- To Identify critical process parameters and ranges for various processing steps.

Pilot Scale Stage

Application of Quality of Conformance (QOC)

- To develop design criteria where the limits are mandated by regulatory agencies (E.g.: content uniformity requirements per USP)
- To process reproducibility, control and uniformity for various processing stages – SPC
- Quantification of process performance and provide a high degree of assurance in meeting limits – Process Capability.
- By combining with QOD principles, provides rationale for manufacturing limits, in-process controls and product specification limits for phase III clinical batches / primary stability batches / pivotal BE batches.

Commercial Scale-up Stage
(Commercial Scale-up trials)

Philosophy:

- Use historical knowledge (studies, data, etc.) from pilot scale process development to justify core manufacturing process, preliminary manufacturing limits, in-process controls and product specification limits.
- Reduced experimentation (reduce the number of factors to be studied based on pilot scale recommendations).

Goals & Objectives:

- Establish manufacturing process at commercial scale and site.
- Identify critical process parameters (targets and ranges) for critical processing stages based on pilot scale process development data.
- Establish process robustness.
- Establish a basis for process validation.
- Eliminate need to validate extremes

Commercial Scale-up Stage
Application of Quality of Design (QOD)

- To understand input-output relationships – empirically, worst case situations, common sense, etc. Most critical elements (E.g.: moisture profile in granulation process, blending time, compression speed, etc.), based on pilot scale studies, will be studied.

- Ensure process integrity via extensive sampling and testing (physical and chemical) – Extensive characterization of various in-process and finished product samples.

- Identify critical process parameters and ranges for various processing steps.

Commercial Scale-up Stage
Application of Quality of Conformance (QOC)

- To process reproducibility, control and uniformity for various processing stages – SPC.

- Quantification of process performance and provide a high degree of assurance in meeting limits – Process Capability.

- By combining with QOD principles, provide rationale for finalizing manufacturing limits, in-process controls and product specification limits for validation batches / regulatory submissions, etc.

Process Validation Stage

Philosophy:

- No experimentation during process validation.
- No evaluation of extremes during process validation. Use historical development data to justify the ranges instead.
- Manufacturing on target.
- 3 successive successful batches.

Goals & Objectives:

- Affirmation of the final manufacturing process developed through pilot scale process development and commercial scale-up trials.
- Prove the accuracy of final process parameters established during development and commercial scale-up.
- Provide basis for routine commercial manufacturing.

Process Validation Stage (contd.)

- Application of Quality of Design (QOD) to:
  - Ensure process integrity via extensive sampling and testing (physical and chemical)
- Application of Quality of Conformance (QOC) to:
  - Assure process reproducibility, control and uniformity for various processing stages – SPC.
  - Quantification of process performance and provide a high degree of assurance in meetings limits – Process Capability.