QbD implementation in Generic Industry:

Are we there yet?

Inna Ben-Anat, Director, Global QbD and Product Robustness,
Teva Pharmaceuticals

Jan 2015

Generic Industry is functioning at a **Rapid Pace**

The Market is very **Competitive**

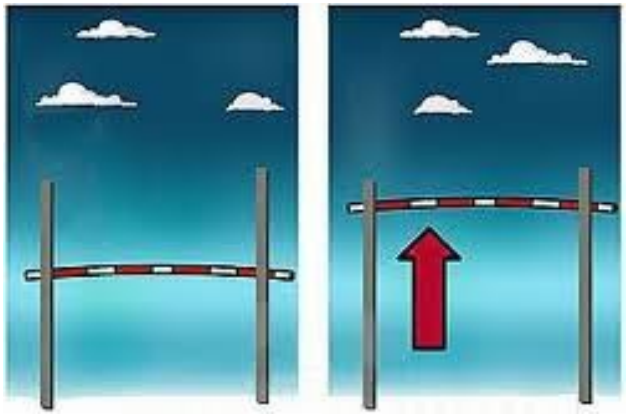
Coke ($1.59)

Pepsi ($1.00)

Generic ($0.79)

Products **Complexity** is growing

The bar for **Quality** of Applications is raising



From our perspective: Patients deserve quality medications

Lawrence X. Yu, Ph.D., Acting Director of FDA's Center for Drug Evaluation and Research's Office of Pharmaceutical Science, discusses the important roles of FDA and drug companies in ensuring quality drug products.

Drug quality -- a shared responsibility

At the end of the day, it's the patients who rely on their medications and who suffer the consequences of poor quality; Providing patients with substandard or contaminated medications is simply unacceptable.

http://www.fda.gov/Drugs/NewsEvents/ucm428298.htm

The ultimate goal-robust supply of highest quality affordable medication for the patient

(~ 80% prescriptions in US are generics)

Quality by Design

Enhanced Product and Process Understanding

Are We There Yet ???

Where we are today with QbD Implementation

Published FDA **Case-Studies**

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Internal Industry's QbD Guidelines

...one you are aware...

- Modified R... QbD Example

http://www.fda.gov/downloads/D... ...entApprovalProcess/HowDrugsareDevelopedandApproved/App... .../AbbreviatedNewDrugApplicationANDAGenerics/UCM28659...

- Immediate Release QbD Exampl...

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM304305.pdf April 2012

✓FDA/GPhA CMC Meeting, May 2013

Review Article

Understanding Pharmaceutical Quality by Design

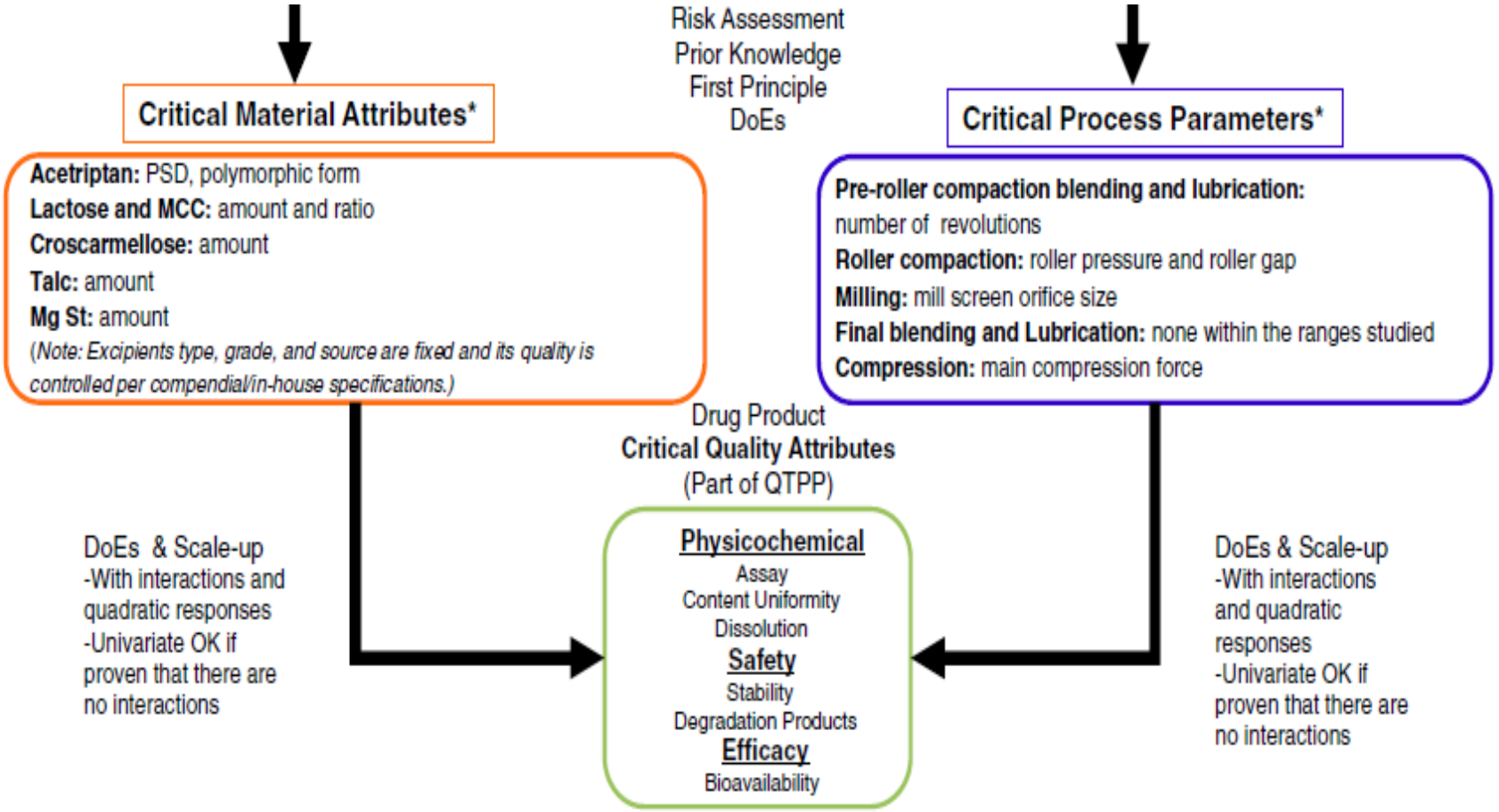
Lawrence X. Yu,[1,6] Gregory Amidon,[2] Mansoor A. Khan,[1] Stephen W. Hoag,[3] James Polli,[3] G. K. Raju,[4,5] and Janet Woodcock[1]

Received 17 November 2013; accepted 24 March 2014

Abstract. This review further clarifies the concept of pharmaceutical quality by design (QbD) and describes its objectives. QbD elements include the following: (1) a quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product; (2) product design and understanding including identification of critical material attributes (CMAs); (3) process design and understanding including identification of critical process parameters (CPPs), linking CMAs and CPPs to CQAs; (4) a control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process; and (5) process capability and continual improvement. QbD tools and studies include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE) and data analysis, and process analytical technology (PAT). As the pharmaceutical industry moves toward the implementation of pharmaceutical QbD, a common terminology, understanding of concepts and expectations are necessary. This understanding will facilitate better communication between those involved in risk-based drug development and drug application review.

KEY WORDS: control strategy; critical quality attributes; pharmaceutical quality by design; process understanding; product understanding.

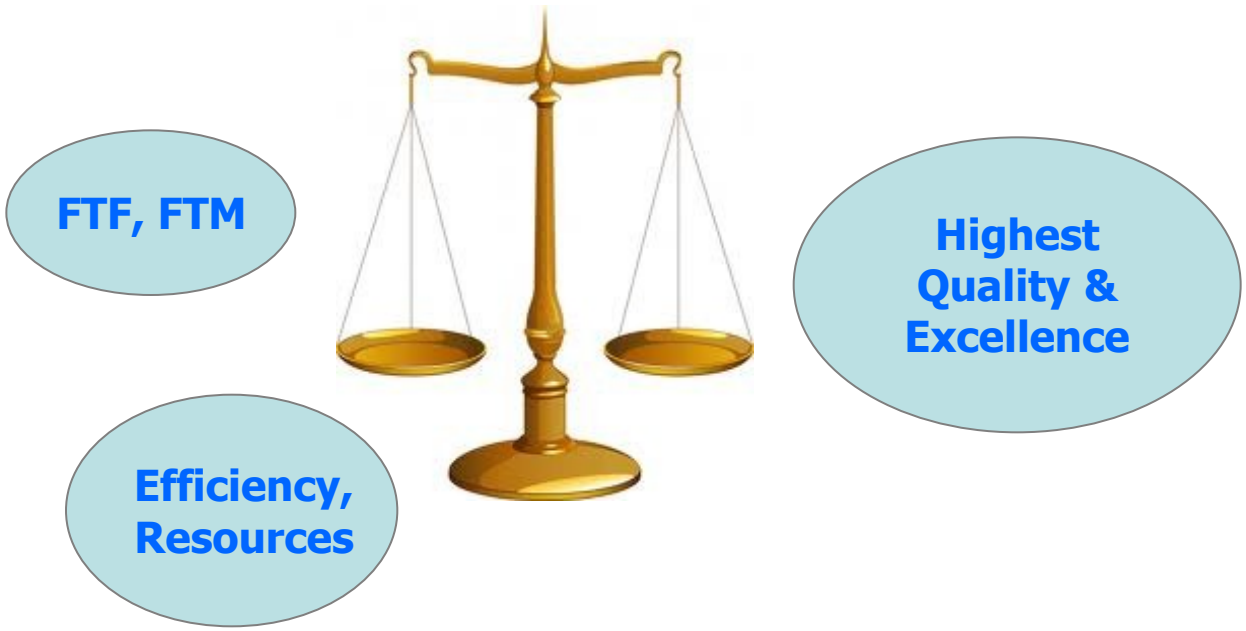
Product and Process Understanding



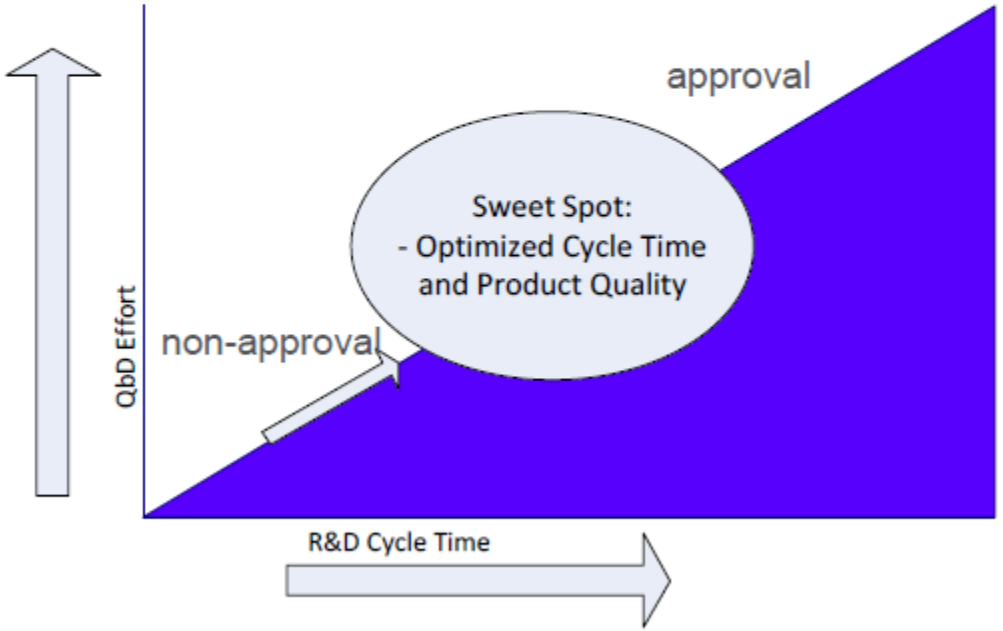
*Conclusion is drawn based upon the ranges studied and the control strategy for other variables (fixed or controlled within the ranges studied)

Fig. 2. Product and process understanding: an example for immediate release dosage forms

QbD for Generics: Finding the right balance between Speed, Efficiency and Excellence



Strategic Perspective on QbD



GPhA Fall Technical Conference
October 27-29, 2014
North Bethesda, Maryland

Michael Kimball
Executive Director, Transdermal Development
Actavis plc
Salt Lake City, Utah

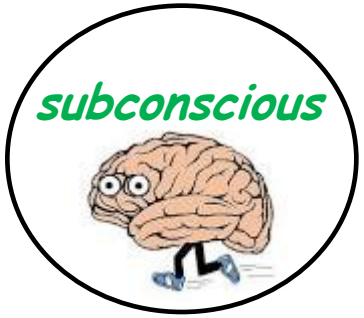
Product Development Outline based on QbD Methodology

Design/ Definitions	• Characterization of the Reference Listed Drug *(RLD)* • Defining Quality Target Product Profile *(QTPP)* • Identification of Critical Quality Attributes *(CQAs)*
Risk Assessment	• Identification and evaluation of potential risks related to Drug Product Components (DS and Excipients – stability and compatibility), Formulation and Manufacturing Process, etc.
Risk Evaluation	• Screening and optimization of formulation and Critical Material Attributes (*CMAs*) • Development of a robust process (DOE for high risk Critical Process Parameters, *CPPs*)
Control/ Implementation	• Establishment of Control Strategies and manufacture of the exhibit batches • Continuous Monitoring and Improvement

Prior Knowledge Management, Risk Assessment Techniques, Statistically Designed Experimentation, Data Management are some of the tools that will assure the desired balance between ***Efficiency and Excellence***

QbD Implementation in Generics:
Where we are today

- QbD format (*content?*) in almost 100% submitted applications
- Follow the QbD implementation guideline as illustrated in published IR/MR case-studies (*sometimes too close?*)
  - Include all five QbD Elements in submission (QTPP, CQAs, Product Design, Process Design, Control Strategy) (*supported by relevant data?*)
- Routinely Perform Risk Assessment and utilize Risk Assessment tools (Cause and Effect diagrams, Risk Ranking, FMEA etc.) (*proactively?*)
- Conduct Design of Experiments-the ultimate tool to demonstrate enhanced product and process understanding (*based on the Risk Assessment? understanding practical significance and interactions?*)
- Enhanced statistics utilization
  - Statistically trend and assess Stability Data
  - Assessing Process Capability, Data-Driven Justification of Specifications (*before CRL is asking to justify/tighten?*)



It is not about the amount of the data,
but its relevance…

Adequate planning of the right/relevant studies based on proactive risk assessment will assure the balance between efficiency and excellence and Right First Time applications

The **'Magic'** of Statistics…..

Joe, can you do your magic with this data we collected from 5 recent OFAT Trials?

Joe, Pharma Statistician

Mike, Formulator

✓ *OFAT trials analyzed statistically won't bring as much insight as DOEs, which are carefully designed to protect against noise, bias and confounding and identify interactions*

"To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of."

-- Ronald Fisher (1938)

New from the **Regulator**….

- Supporting Regulatory Landscape
  - ✓ GDUFA - encourages RFT High Quality Submissions
  - ✓ Updated QbR - formalizes QbD milestones and format
  - ✓ Shift in Complete Response Letters questions 'culture' toward Product and Process Understanding
  - ✓ Future ICH Q12 –Lifecycle Management

Next

What does **GDUFA** mean for the Industry

Strategy

- What worked in the past will not work under GDUFA! **Transformational Change**!
- **Increased focus on Quality:** Develop robust products; submit high quality ANDA and maintain high quality in manufacturing; Quality will either be a differentiator or a barrier
- Requires complete **visibility of the suppliers** ; APIs, third party manufacturers, testing sites, packaging sites, etc
- Higher **barrier to entry in the market** - building the quality into the systems.

Execution

- **Robust product & process**: Implementation of Full Quality by Design
- Ensure 100% alignment and **training** of all R&D and Regulatory staff on new Guidance's and GDUFA requirements.
- Further **collaboration** among the network from product identification through commercialization

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MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH **MAPP 5015.10**

POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL SCIENCE

Chemistry Review of Question-based Review (QbR) Submissions

BACKGROUND

- QbR was developed for the assessment of generic drug applications (i.e., ANDAs) in response to FDA's initiative for Pharmaceutical cGMP's for the 21st Century. It uses QbR experiences from other CDER components (e.g., CDER MAPP 4000.4 *Clinical Pharmacology and Biopharmaceutics Review Template*), as well as other regulatory authorities (e.g., Health Canada) that use the quality overall summary (QOS) as a foundation for the primary chemistry review document.

12. What formulation development studies were conducted? What attributes of the drug substance, excipients and in-process materials were identified as critical and how do they impact the drug product CQAs?

16. For each of the potentially high risk manufacturing unit operation:

a) What input material attributes and process parameters were selected for study and what are the justifications for the selection?
b) What process development studies were conducted? Provide a summary table listing batch size, process parameter ranges, equipment type and estimated use of capacity.
c) What process parameters and material attributes were identified as critical and how do they impact the drug product CQAs?
d) How were the process parameters adjusted across lab, pilot/registration and commercial scale? What are the justifications for any changes?

15. What is the potential risk of each process step to impact the drug product CQAs and how is the risk level justified?

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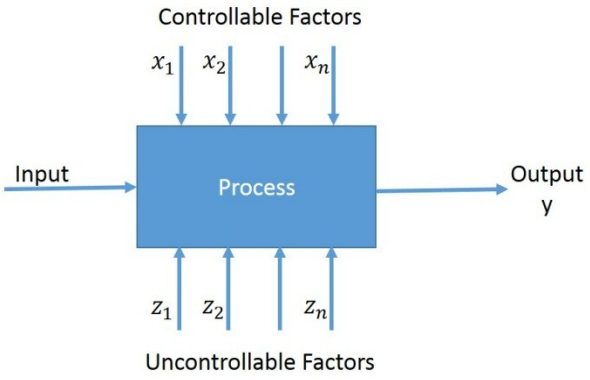
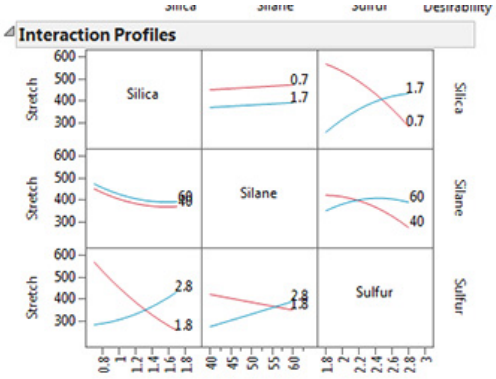
Example of CRL Comment

3. We note that you used one-factor-at-a time (OFAT) approach for formulation and process development. This approach is viable for feasibility/screening study. However, it is not efficient and may miss the variable interactions on drug product critical quality attributes (CQAs). For future submission, we strongly encourage you to use multivariate experimental design (DOE) to study the formulation and process when there are more than one high risk variables involved.





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ICH Q12 Final Business Plan

ICH
harmonisation for better health

Final Business Plan
Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
dated 28 July 2014
Endorsed by the ICH Steering Committee on 9 September 2014

In summary, the main drivers include: a more strategic approach to Lifecycle Management (LCM) across the product lifecycle, an opportunity to focus on science and risk based approaches for the assessesment post-approval changes with the appropriate level of regulatory oversight, encouraging Companies to develop and register more enhanced Quality by Design (QbD) approaches (supporting fuller implementation of Q8, Q9, Q10 and Q11), encouraging and providing companies with tools to introduce more innovative approaches to manufacturing across the ICH regions.

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How Do We (Industry) Measure Success

Defining **QbD Success**: Metrics and KPIs examples

- **Short Term KPIs examples:**
  - ✓ % QbD Submissions (include 5 elements outlined by FDA)
  - ✓ % Submissions contain Formulation/Process DOE-enhanced approach
  - ✓ % Submissions utilizing PAT tools-enhanced approach
- **Long Term metrics examples:**
  - ✓ Success rate of scale-up, validation and launch
  - ✓ Overall products quality and robustness improvement
  - ✓ Shorter review cycle/fewer DL rounds-RFT Submission

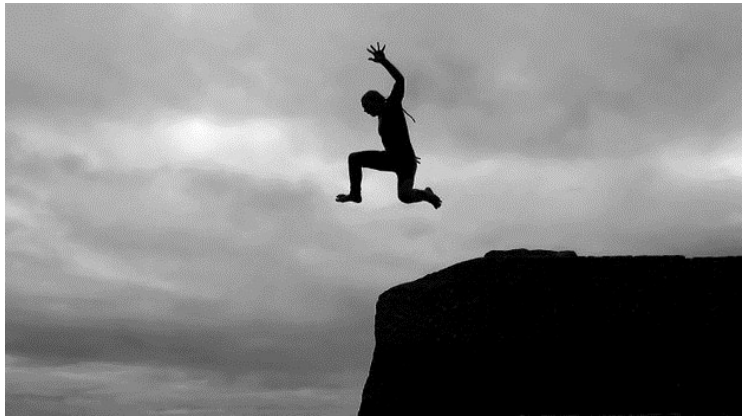
Where we want to be…

How will we get there…

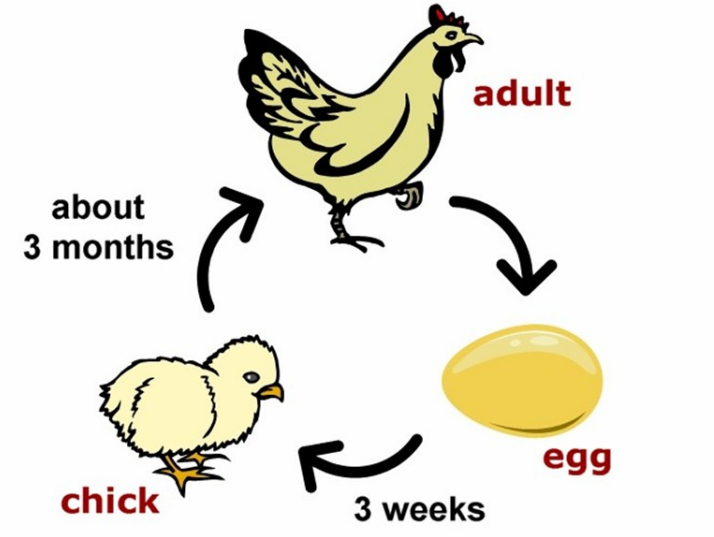
Areas of Additional Focus

- PAT Implementation and application
- More hands on experience with QbD application for additional dosage forms (injectables, patches, films, etc.)
- Leveraging prior knowledge efficiently: effective knowledge management platform, historical data mining and filtering capabilities
- Leverage QbD based development throughout product validation and commercialization-lifecycle approach
  - Manage Risk Assessment (QRM) throughout product lifecycle
  - Leverage QbD-gained knowledge through CPV stage
  - Data collection and analysis automation

QbD doesn't end once file is submitted



It's a lifecycle approach



Implementation of QbD Principles post-submission

- Risk Assessment, DOE and Historical Data Mining techniques utilization
- Product Robustness initiatives
- CPV (Continuous Process Verification)

Statistical Tools to Support product life-cycle (PDA)

Table 6.2-1 Statistical Methods and the Typical Stages at Which They Are Used

Statistical Tool	Stage 1 Process Design	Stage 2 PQ	Stage 3 CPV
Descriptive Statistics – Mean, standard deviation, etc.	X	X	X
Statistical Process Control Charts	X	X	X
Statistical Power and Sample Size Determination	X	X	X
Process Capability Study and Capability Indices	X	X	X
Design of Experiments	X		
Measurement Systems Analysis (Gauge R&R)	X		
Robust Process Design / Tolerance Analysis / Taguchi Methods	X		
Multi-Vari Chart	X		
Regression and Correlation Analysis	X		
Analysis of Variance (ANOVA)	X	X	X
Levene/Brown-Forsyth, Bartlett, F_{max} Tests for Variation	X	X	X
Hypothesis Tests / Confidence Intervals	X	X	X
Pareto Analysis	X		X
Acceptance Sampling Plans		X	X
Normal and Nonparametric Tolerance Intervals		X	X

https://store.pda.org/ProductCatalog/Product.aspx?ID=2395

R&D Stage: Formulation/Process optimization, DOE

Response Y

Summary of Fit

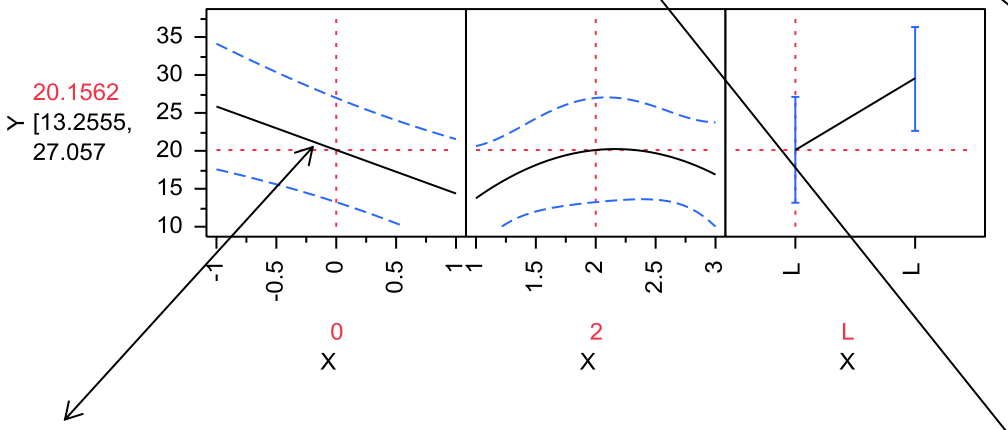
RSquare	0.999117
RSquare Adj	0.995584
Root Mean Square Error	0.655
Mean of Response	21.695
Observations (or Sum Wgts	6

Variability explained

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
X1	-5.76375	0.283623	-20.32	0.0313 *
X3[L1]	-4.75375	0.283623	-16.76	0.0379 *
X2*X2	-4.8225	0.567247	-8.50	0.0745
X2(1,3	1.5675	0.3275	4.79	0.1311

Prediction Profiler



Relationship

Relationship

Factors' significance

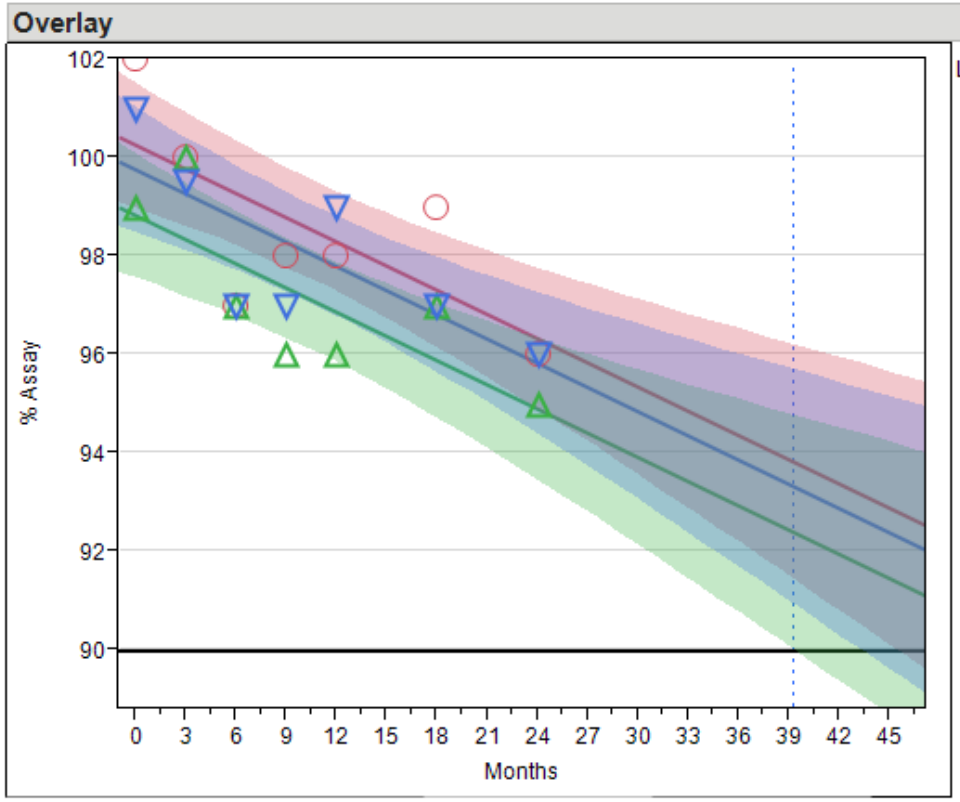
CMAs and CPPs are identified and their impact on CQAs is understood;

Product Robustness is designed in

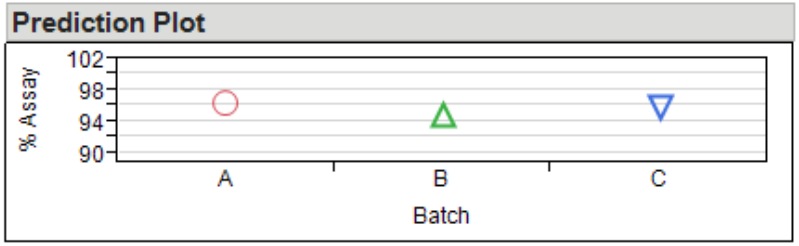
and assessed with simulation tools

'All examples are for illustration purposes only'

Submission Stage: Stability Data Assessment, 3 Submission batches



Residual Plot Inverse Prediction Prediction Graph



Predicted value of % Assay at Months=24

Stability Tests

The best model accepted at the significance level of 0.25 has Different intercepts and Common slopes. The model suggests the earliest crossing time at 39.33263 with 95 percent confidence. ICH Guidelines indicate an expiration time of 39.33263

Display	Intercept	Slope	Earliest Crossing Time
○	Different	Different	
◉	Different	Common	39.33263
○	Common	Common	42.67992

Model Comparisons

Source	DF	SS	Mean Square	F Statistic	Prob>F
A	4	7.35978	1.839945	1.014625	0.4310
B	2	7.357143	3.678571	2.028523	0.1661
C	2	0.002638	0.001319	0.000727	0.9993
D	15	27.20135	1.813423		
E	6	201432	33572.01		

Legend

Source		Intercept	Slope	Intercept	Slope
A		Different	Different	Common	Common
B		Different	Common	Common	Common
C		Different	Different	Different	Common
D	Residual				
E	Whole Model				

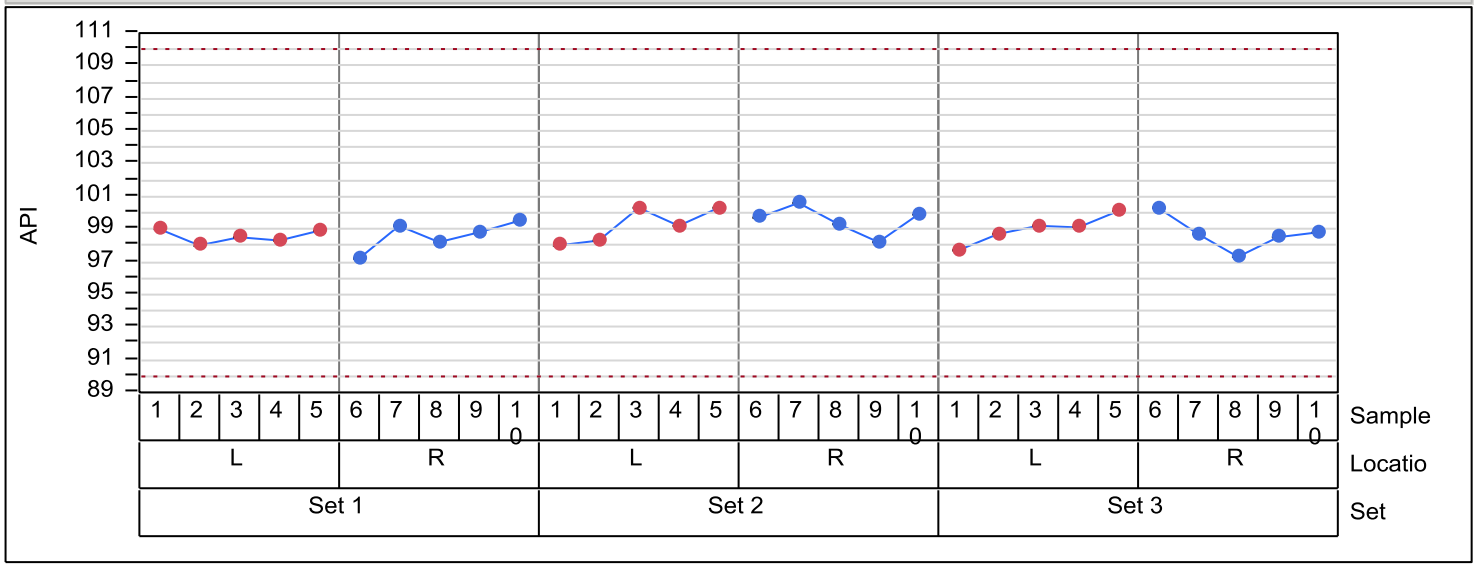
Stability Platform assures compliance with ICH requirements and provides comprehensive overview of stability data assessment and batches poolability

'All examples are for illustration purposes only'

Submission/Process Design Stage: Uniformity VCA (Variance Components Analysis)

Variability Gauge

Variability Chart for API %



Partial confounding of effects detected. Reverting to REML estimates.

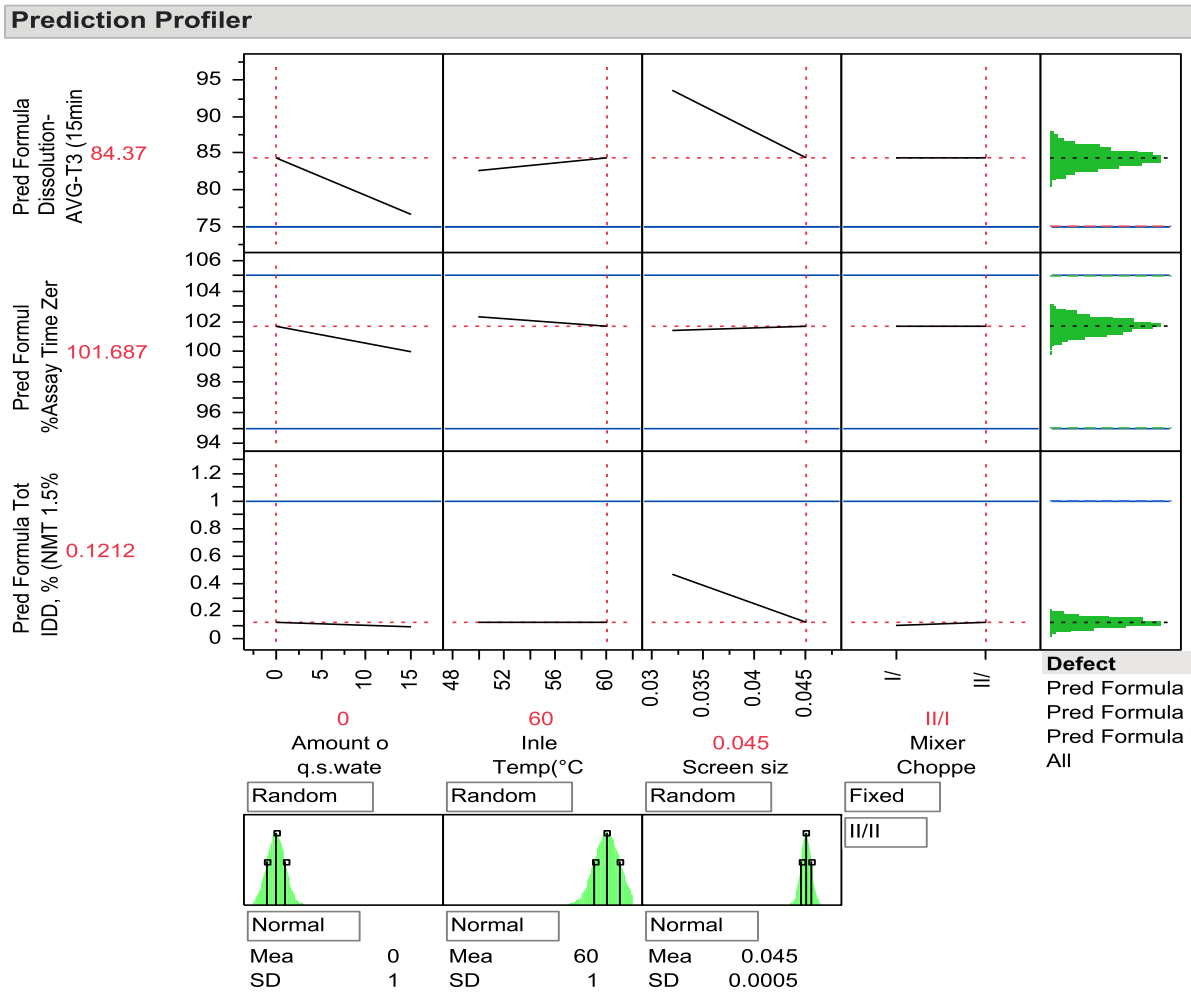
Variance Components

Component	Var Component	% of Total	20 40 60 80	Sqrt(Var Comp)
Set	0.11188889	13.2		0.33450
Location	0.00000000	0.0		0.00000
Sample	0.11577778	13.7		0.34026
Within	0.61844444	73.1		0.78641
Total	0.84611111	100.0		0.91984

VCA platform provides enhanced uniformity and process robustness assessment already at R&D stages

'All examples are for illustration purposes only'

Development/Process Design Stage: Simulation Tools to evaluate Process Robustness at pilot scale



Distribution of the predicted output

Defect	Rate	Mean	SD
Pred Formula Dissolution-AVG-T3 (15min	0	84.36	1.22344
Pred Formula %Assay Time Zero	0	101.702	0.51633
Pred Formula Total IDD, % (NMT 1.5%)	0	0.12064	0.03283
All	0		

Predicted OOS rate

Estimated Process Variability

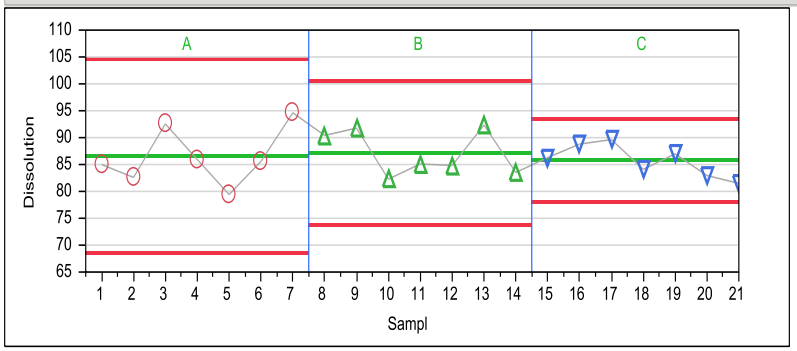
Estimated Analytical Variability

'All examples are for illustration purposes only'

Continuous Process Verification (CPV)

Control Chart

Individual Measurement of Dissolution %

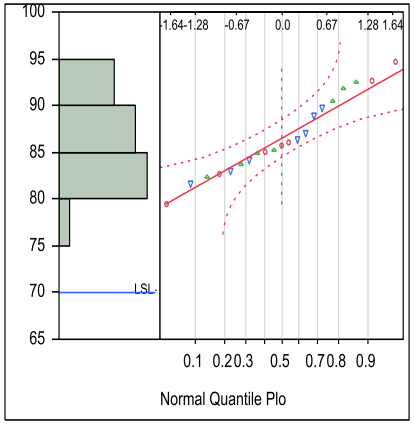


Phase Limits

Phase	LCL	Avg	UCL
A	68.50957	86.52997	104.5504
B	73.75588	87.178	100.6001
C	78.11865	85.7507	93.38275

Distributions

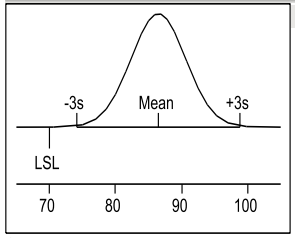
Dissolution %



Capability Analysis

Specification	Value	Portion	% Actual
Lower Spec Limi	70	Below LSL	0.0000
Spec Target	.	Above USL	.
Upper Spec Limi	.	Total Outsid	0.0000

Long Term Sigma



Sigma = 4.1140

Capability	Index	Lower CI	Upper CI
CP	.	.	.
CPK	1.336	0.899	1.768
CPM	.	.	.
CPL	1.336	0.899	1.768
CPU	.	.	.

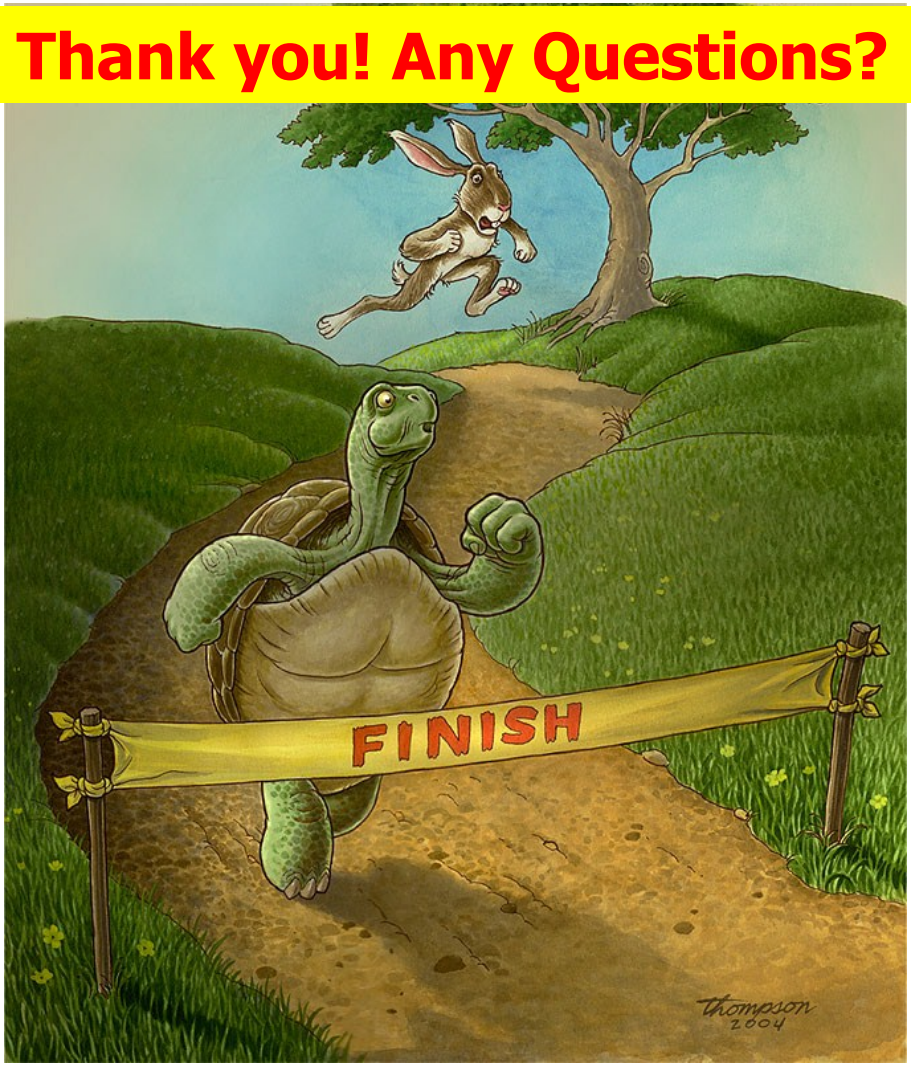
Portion	Percent	PPM	Sigma Quality
Below LSL	0.0031	30.7078	5.507
Above USL	.	.	.
Total Outsid	0.0031	30.7078	5.507

SPC as main tool for CPV stage and continuous improvement throughout life-cycle

'All examples are for illustration purposes only'

Are We There Yet?

Thank you! Any Questions?



Slow and Steady Progress …