Regulatory landscape changes and statistical methodologies as enabling tools to efficiently cope with new requirements

Inna Ben-Anat, Director, Head of QbD and Product Robustness, Teva Pharmaceuticals USA
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.
We need to ask ourselves:

Are you too busy to improve?

No thanks!
We are too busy
The ultimate goal—robust supply of highest quality affordable medication for the patient
(almost 80% prescriptions in US are generics)
Focus on patient and QTPP:

**Guidance on Size and Shape** FDA Draft Guidance 2013: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules

Raising the bar, Stability Guidance:

**Implementing ICH Q1 Guidance for ANDA s Primary Batches, 6M Stability Data for Submission**

Raise the Bar at Filing for Product & Submission Quality:

**RTR Guidance, October 2013**

Risk Based Review:

**OGD/OPQ Update, GDUFA**

Pharmaceutical Quality Systems:

**GMP Quality Metrics Initiative**
### Quality by Design

1. Clearly defining the intended purpose of the future developed product and design this product to fit its purpose

2. Understanding what attributes of this product are critical so it (product) will keep serving its intended purpose

3. Enhanced understanding ‘what’ impacting the critical quality attributes and ‘how’ (materials, process, packaging etc) ; define control strategies so that the intended purpose of the product will reproducibly maintain its integrity

### Generic Industry

1. Reproducibly Making “A drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use”

2. Providing uninterrupted supply of high quality and affordable medication to our patients

3. Efficiency and Speed
QbD for Generics: Finding the right balance between Speed, Efficiency and Excellence
Why quality-by-design should be on the executive team’s agenda

Ted Fuhr, Michele Holcomb, Paul Rutten

Better practices in product and process development could raise the profits of pharmaceutical companies by up to 20%. Now is the time to implement Quality by Design.
Why Quality-by-Design (Benefits)?

➢ Adoption of QbD stems from the commitment to deliver a quality product to meet customer’s needs

  – Modern risk and science-based approach
  – ‘Benefits’ are a byproduct

“We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear...” – George W. Merck (1950)
Where we are today with QbD implementation among generic industry......
Published Case Studies for IR and MR products

FDA/GPhA CMC Meeting, May 2013

Hope you are aware…

➢ Modified Release QbD Example


➢ Immediate Release QbD Example

Draft QbR—Updated 09/06/12

The following is a proposed draft to update the current set of questions provided within the question-based review (QbR) framework by the Office of Generic Drugs. Please send your feedback or suggestions to GenericDrugs@FDA.HHS.Gov.

2.3.P.2 Pharmaceutical Development

4. What are the characteristics of the RLD Product?

5. What are the elements, targets and justifications of the Quality Target Product Profile (QTPP)?

6. For each quality attribute of the drug product, what is the target and how is it justified? How were the critical quality attributes (CQAs) selected?
Where we are? ICH Regulatory toolbox

- ICH Q8, Q9 and Q10; Q11
- ICH- IWG Questions and Answers
  - Knowledge Management, Design Space, Real Time Release, Control Strategy and Pharmaceutical Quality System
- Points to consider on:
  - Criticality of Quality Attributes and Process Parameters
  - Control Strategy
  - Level of Documentation R/A and DoE

Already here, December 2011

- Additional Points to consider to come:
  - Design space, modelling, process validation/continuous process verification

Is QbD a Mandate for Generics? FDA Responds to Confusion

Posted on 10 July 2012. Tags: fda, generic drugs

By Paul Thomas, Senior Editor

Last fall, FDA’s Lawrence Yu, deputy director for science and chemistry in the Office of Generic Drugs, said the following:

“As we’ve said many, many times, FDA Office of Generic Drugs expects QbD applications starting January 2013. You heard right, full implementation of QbD in January 2013.”

The “full implementation” part got people buzzing, arguing, and feeling a bit unprepared. More than half a year later, there is still confusion. Was Yu saying that QbD-based submissions will be mandatory for all generics manufacturers come January 1?
Brief Refresher on main 4 steps of QbD Implementation (up to submission stage):

1. **Product Design**
2. **Risk Assessment**
3. **Mitigation Strategy Studies**
4. **Control Strategy**
QbD Guide for Generics: Step 1 - Product Design

- RLD Characterization
- Quality Target Product Profile
- Critical Quality Attributes

What is a Quality Target Product Profile (QTPP)

**ICH Q8(R2) Definition:** A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy.

**QTPP-Designs and defines the function of the product ...**

**TPP:** labeled use, safety and efficacy

**QTPP:** quality characteristics to ensure safety and efficacy as promised in the label

GPhA/FDA CMC Workshop, May 2012
### QTPP (Case-Study)

<table>
<thead>
<tr>
<th>Component</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage Form</td>
<td>Tablet</td>
<td>Pharmaceutical equivalence to RLD</td>
</tr>
<tr>
<td>Administration Route</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Dosage Design</td>
<td>Immediate release tablet</td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>X and Y mgs</td>
<td></td>
</tr>
<tr>
<td>Bioequivalence</td>
<td>AUC and Cmax match RLD under food</td>
<td>Bioequivalent to RLD</td>
</tr>
<tr>
<td>Appearance</td>
<td>Both: Brown to orange elegant film coated tablet. Dimensions similar to RLD. X mg: round; Y mg: oval</td>
<td>Marketing requirement; Needed for patient acceptability</td>
</tr>
<tr>
<td>Identity</td>
<td>Positive for API</td>
<td>Needed for labeled claim &amp; therapeutic efficacy</td>
</tr>
<tr>
<td>Assay</td>
<td>100% of label claim</td>
<td>Needed for therapeutic efficacy</td>
</tr>
<tr>
<td>Impurities</td>
<td>Specified and unspecified impurities meet ICH Q3B.</td>
<td>Needed to ensure safety</td>
</tr>
<tr>
<td>Disintegration</td>
<td>Comparable disintegration time as RLD in appropriate media at room temperature</td>
<td>Pharmaceutical equivalence to RLD (possible route of administration as suspension)</td>
</tr>
<tr>
<td>Content Uniformity</td>
<td>AV &lt;15.0 (tested by weight and time)</td>
<td>Targeted for consistent clinical effectiveness</td>
</tr>
<tr>
<td>Residual solvents</td>
<td>Complies with USP &lt;467&gt;</td>
<td>Regulatory requirement. Needed to ensure safety</td>
</tr>
<tr>
<td>Dissolution</td>
<td>USP Apparatus II, 50 rpm, 1000 mL 0.1M HCl, 37°C. NLT 85Q is dissolved in 45min</td>
<td>Regulatory requirement</td>
</tr>
<tr>
<td>Stability</td>
<td>NLT 24 month shelf life</td>
<td>Needed for commercialization</td>
</tr>
<tr>
<td>Container closure system</td>
<td>HDPE bottles with Child Resistant (CR) Caps and appropriate desiccants , if required</td>
<td>Needed for safety and commercial requirements</td>
</tr>
</tbody>
</table>

**Potential CQAs**
Identification of Critical Quality Attributes (CQAs) in Product Development

Decide whether the quality attribute is critical to product safety and/or efficacy.

- Yes → CQA
  - Decide whether the CQA may be impacted by formulation and process variation during development.
    - No or low potential → Not a CQA
    - Yes → CQA has high potential for change
      - Yes → CQA will be used in risk assessment analysis to develop the formulation and process.
      - No or low potential → CQA, but not used in risk assessment

GPhA/FDA CMC Workshop, May 2012
Step 2 - What are the potential Risks

Definition

ICH Q9 defines risk as “Risk is commonly understood to be a combination of the Probability of Occurrence of Harm and the Severity of the Harm.”

Process Understanding: Linking CMAs and CPPs to CQAs

\[ CQAs = f(CPP_1, CPP_2, CPP_3, ..., CMA_1, CMA_2, CMA_3, ...) \]
Step 2 - What are the potential Risks

Risk Assessment Defines the Development Strategy

What are the Risks?...
- API
- Excipients
- Formulation and Process
- Equipment
- Testing
- Packaging
- ...

How do we stay efficient
- Effective Prior Knowledge utilization and management
  - Generic Industry has a lot of information and in-house knowledge available
    - Data bases of pre-created Ishikawa diagrams in order to harmonize and streamline the Risk Assessment process
    - Historical data-mining
A Typical Manufacturing Process for Tablets...

For a process involving the above unit operations we may end up with over 100 potential CPPs.

How do we manage this?
High Shear Wet Granulation: > 40 potential CPPs…

High Shear Wet Granulation
Fish-Bone Diagram

**Material**
- initial LOD of materials
- solubility of materials
- density of materials
- formulation
- binder solution temperature
- binder solution viscosity
- granulation solution (water or solvent based)

**Processing**
- bowl jacket temperature
- granulation end point
- number of solution additions
- post mixing time
- wet massing time
- spray pattern
- solution addition rate
- amount of solution
- binder solution addition method (pump, pressure vessel, pour)
- chopper speed - wet granulation
- impeller speed - wet granulation
- pre-blend mixing time
- chopper speed - preblend
- impeller speed - preblend
- percent loading in equipment

**Environment**
- room temperature
- room humidity
- amount of binder
- binder solution temperature
- granulation solution (water or solvent based)

**Man**
- material charging technique
- operator observation for end-point determination
- degree equipment cleaned between sub-batches

**CQAs**
- top or bottom mounted impeller
- equipment size/volume
- length of spray tubing
- diameter of spray tubing
- height of nozzle
- type of nozzle
- lag time for impeller to reach target speed
- orientation of nozzle
- number of blades for impeller
- geometry of impeller and chopper
- number of blades for chopper

**Equipment**
- bowl jacket temperature
- equipment measurement (KW, % torque, amps)
Prior Knowledge Utilization

Blending Unit Operation

4 critical variables are left for assessment, the rest are kept at constant and monitored

Design Variable

Prior Experience/Fixed

Justify!!
Efficient and Informative DOE: $CQAs = f(CPPs, CMAs)$

- **How do we stay efficient**
  - Effective Prior Knowledge Utilization
    - What do we **vary** and what do we **fix**?
    - What **target** and **range** do we evaluate and **why**?
    - What **statistical model** do we use and **why**? (Can we assess what interactions are most likely to occur? Can we assess what factors would have non-linear relationship with the response?)
  - Modern DOE techniques for efficient yet powerful designs (D-Optimum, I-Optimum)
  - Monte Carlo Simulations to assess the process robustness using historical data to assess expected variability
It is not about the amount of the data, but its relevance...
Questions to ask ourselves:

1. Did we evaluate the impact of CMAs and CPPs on CQAs? Did we find any interactions? What do they mean for us?
2. Do we have a robust and reproducible process? Do we know the impact of raw materials variability? Did we identify potential sources of variation?
3. Did we establish meaningful In Process and Release specifications?
4. Did we address scale-up challenges?
5. .................................................................
What is Control Strategy?

- A concise summary of critical material attributes (CMA) / critical process parameters (CPP)
- Acceptable operating range for CMA and CPP
- Requirement by the regulatory agencies
- Assurance that CQAs are met
QbD doesn’t end once file is submitted

It’s a lifecycle approach
Statistical Tools to Support product life-cycle

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

And enable efficiency!
Efficient and effective novel designs provide flexibility needed at R&D stage and assure maximum reliable information from minimum trials.
R&D Stage, Formulation/Process optimization, DOE

CMAs and CPPs are identified and their impact on CQAs is understood; Product Robustness is designed in and assessed with simulation tools.

Variability explained

Factors’ significance

Relationship

Response Y

Summary of Fit

| Term        | Estimate | Std Error | t Ratio | Prob>|t| |
|-------------|----------|-----------|---------|------|
| RSquare     | 0.999117 |           |         |      |
| RSquare Adj | 0.995584 |           |         |      |
| Root Mean Square Error | 0.655 |       |         |      |
| Mean of Response | 21.695 |       |         |      |
| Observations (or Sum Wgts) | 6 |       |         |      |

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

‘All examples are for illustration purposes only’
Simulation Tools to evaluate Process Robustness already at **lab/pilot scale**

**Estimated Process Variability**

**Estimated Analytical Variability**

--

\[\text{Distribution of the predicted output}\]

<table>
<thead>
<tr>
<th>Defect</th>
<th>Rate</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pred Formula Dissolution-AVG-T3 (15min)</td>
<td>0</td>
<td>84.36</td>
<td>1.22344</td>
</tr>
<tr>
<td>Pred Formula %Assay Time Zero</td>
<td>0</td>
<td>101.702</td>
<td>0.51633</td>
</tr>
<tr>
<td>Pred Formula Total IDD, % (NMT 1.5%)</td>
<td>0</td>
<td>0.12064</td>
<td>0.03283</td>
</tr>
<tr>
<td>All</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‘All examples are for illustration purposes only’
Submission Stage, Stability Data Assessment, 3 Submission batches

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’
3 submission batches - Blend and Content Uniformity
VCA (Variance Components Analysis)

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

Partial confounding of effects detected. Reverting to REML estimates.

Variance Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Var Component</th>
<th>% of Total</th>
<th>20 40 60 80</th>
<th>Sqrt(Var Comp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set</td>
<td>0.111888889</td>
<td>13.2</td>
<td></td>
<td>0.33450</td>
</tr>
<tr>
<td>Location</td>
<td>0.000000000</td>
<td>0.0</td>
<td></td>
<td>0.000000000</td>
</tr>
<tr>
<td>Sample</td>
<td>0.115777778</td>
<td>13.7</td>
<td></td>
<td>0.34026</td>
</tr>
<tr>
<td>Within</td>
<td>0.618444444</td>
<td>73.1</td>
<td></td>
<td>0.78641</td>
</tr>
<tr>
<td>Total</td>
<td>0.846111111</td>
<td>100.0</td>
<td></td>
<td>0.91984</td>
</tr>
</tbody>
</table>

‘All examples are for illustration purposes only’
Risk Based approach for specifications evaluation, pre/post submission stage

Tightening Assay spec from 90.0-110.0 to 95.0-105.0:

Available Data:
- AVG=98.8
- STDEV =2.1

Accept new spec??

‘All examples are for illustration purposes only’
Review Letters and Specification Revisions assessment

Summary Statistics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>μ</td>
<td>98.80888</td>
<td>97.84284</td>
</tr>
<tr>
<td>Dispersion</td>
<td>σ</td>
<td>2.122572</td>
<td>1.6236523</td>
</tr>
</tbody>
</table>

Cpk 0.60 (<1.33)
~5% long term OOS (!)

- Reduce Analytical Method Variability
- Reduce Process variability
- Center on target

All examples are for illustration purposes only
Continuous Process Verification (CPV) - Commercial Stage

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

‘All examples are for illustration purposes only’
Summary

- Generic Industry has accomplished great progress with QbD implementation
- There are many guidelines and tools published to guide the industry
- Effective utilization and management of prior knowledge and risk-based approach is a key to successful QbD implementation in generics
- Statistical Tools and Methodologies are great enablers to support new regulatory requirements effectively and efficiently
- Life-Cycle approach is critical to gain the true benefit of QbD implementation
- The ultimate goal is clear: robust supply of highest quality affordable medication for the patient