2nd FDA/PQRI Conference on Advancing Product Quality

Generic Pharma Perspective on the Identification of Critical Quality Attributes and Critical Process Parameters

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Consumer Healthcare R&D

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Perrigo Company plc

Mandate of QbD for the Generic Pharmaceutical Industry
  - Pharmaceutical Development Differentiators - Generic vs. Innovator
  - Impact to ANDAs

Implementation Perspectives
  - Strategic Considerations
  - Process Steps to Achieve Identification of CQAs and CPPs

Case Study
Global Presence
 Positioned to Capture Expanding Global Healthcare Needs

-$5B
 In Sales*

>80
 Markets

31
 Operating Locations

~ 13K
 Employees

>22.8K
 SKUs

>6K
 Formulations

*CY15 Pro Forma, Includes only 9 months for Omega acquisition translated at €1:$1.09
Our Capabilities make Perrigo One of the World’s Leading Pharmaceutical Development & Manufacturing Organizations

**Capabilities**

- **47 Billion** oral solid doses/year
- **3 Billion** liquid/cream doses/year
- **6,000+** formulations
- **23,000** SKUs
- **Launching more than 1 new product/week**
- **Investing $120-$180M/year in new capabilities**

- Tablets
- Capsules
- Solutions
- Suspensions
- Sprays (Nasal)
- Suppositories
- Creams/ointments
- Powders
- Lozenge
- Foam
- Aerosols
- Gums
- Injectables
- Spot-on pesticides
- Extruded pellets
Every second of every day, somewhere in the world, nearly 1,600 people will use a Perrigo product
“80% of prescriptions are being filled with generic products and branded drugs coming off patent every day.”

“There is a more crucial need to develop more efficient, reliable, and versatile manufacturing methods.

“Complexity of pharmaceuticals is rapidly increasing...”

“Quality by design is an essential part of the modern approach to pharmaceutical quality.”

“In order for quality to increase, it must be built into the product.”

Generic Manufacturers Need to be Full Participants in FDA’s Pharmaceutical Quality for the 21st Century Initiative

“An initial investment is necessary to achieve the cost effective manufacturing of the Future.”

“Implementation of QbD is essential to ensuring the availability of affordable, high quality generic drugs.”
Pharmaceutical Product Development Timelines to Market

**Originator (NDA)**

- Start
- Animal Testing
- IND Submission
- Phase I Trials
- Phase II Trials
- Phase III Trials
- NDA Filing
- Review Time
- Approval

- ~ 8 years CMC development window

**Generic (ANDA)**

- Start
- Product Development / Pilot BE
- Exhibit Batches
- 6 mos. Stability / Pivotal BE
- ANDA Filing
- Review Time
- Approval

- ~ 2 years CMC development window

FTF or FTM
CMC product development is *always* on the critical path, thereby forcing a generic firm to be very efficient with QbD development processes (including identification of CPPs and CMAs)

- **Documented prior knowledge**
  - Internal data mining
  - Research articles, review papers, patents or reference books
  - Reference Listed Drug (RLD) labeling**

- **Risk assessment**
  - Evaluation
  - Mitigation
  - Control Strategy with Justification

*Predominant early adopters were generic pharma’s 85% vs. 14%: *Generic Industry Has Made Progress Implementing QbD / “The Gold Sheet”* February 28 2013

**QTPPs are typically already established by the RLD (unless new Rx to OTC product)
FDA Review Focus

- Characterization of the Reference Product and Materials
- Design of Product & Process
- Pivotal Bio-batch
- Bioequivalence Study
- Commercial Product Manufacture

API DMF Critical Quality Attributes

- QTPPs
- CQAs
- product design (CMAs) & process (CPPs) understanding
- control strategy

QbD is a development process
QbD elements must be integrated into the development process
“I think you should be more explicit here in step two.”

from *What’s so Funny about Science?* by Sidney Harris (1977)
Perrigo’s Approach Used to Implement QbD

- Risk analysis prior to development work
- Additional experiments / DOE’s
- Training / Culture

FDA Expectations / Feedback

- Review Requirements
- Timing

Updating Development Processes / Procedures

- Using the language of QbD
- Supporting / Executing DOE’s
- Training / Culture

Industry Understanding / Perspective

- Viewing prior knowledge as an asset
- How to....

Evaluating / Updating Business Models

- Providing resources to support enhanced product & process understanding
- People, Materials, Equipment, Technology

Education within organization

Implementation of QbD has been both **Technical** and **Strategic**
Available Tools / Resources

- **MaPP 5015.10 (QbR)** – published November 2014
  - Revised to better capture QbD expectations
  - Reviewer Companion Documents contains additional details for what the applicant should provide for each question

- **Others:**
  - ICH Q1 (A-E): Stability Guidances
  - ICH Q11: Development and Manufacture of Drug Substances
  - USP <1059> Excipient Performance
Perrigo Implementation – *What’s Been Done*

Created a common QbD vision with processes & structured thinking...

**Defined / Updated Development Cycles**
- Clear targets defined throughout development
- Target defined at project initiation
- Risk Assessments drive development work
- Improved processes for data & documentation compilation
- Enhanced Statistical application

**Enhanced Governance**
- Drives discipline & consistency
- Increases awareness & transparency of technical risks
- Input by stakeholders & key participants (cross-functional)

**Invested in training & processes that are sustainable, not individual based**
Perrigo Customized Drug Development Process

Custom interactive platform for integrating development process flows with templates, tools, guidance documents, and procedures

Supports:
• Enhanced data & documentation compilation
• Alignment across multiple developing sites
• Clear expectations for what is required within each development phase
• Improved access and transparency to development data & information
• Technical Governance with awareness of risks / risk management
Drug Product Development through a QbD Process (Identification of CQAs, CPPs & CMAs)

QTPP identified based on the:
• Clinical and pharmacokinetic characteristics of RLD
• RLD Product label
• In-vitro drug release and physicochemical characteristics

<table>
<thead>
<tr>
<th>Quality Target Product Profile (QTPP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTPP Element</td>
</tr>
</tbody>
</table>

Critical Quality Attributes (CQA):
• From the QTPP, Quality Attributes (QAs) of the drug product will be identified

<table>
<thead>
<tr>
<th>Drug Product Critical Quality Attributes (CQA's) Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Attributes of the Drug Product</td>
</tr>
</tbody>
</table>
CQAs are the most important measurable product attributes that are used to make design & optimization decisions and to identify CMAs & CPPs later in development.
Relationship of CMAs, CPPs & CQAs

CPPs
(Process Inputs)

CMAs
(Material Inputs)

Pharmaceutical
Unit Operation

CQAs
(Intermediate or
Final Product)

Note: A CQA of an output may become a CMA if it becomes an input material of another unit operation.

Risk Assessments connect CQAs to the CMAs and CPPs and are the basis for identifying Control Strategies
**Identification of CPPs**

*Definition:*
A process parameter (PP) whose variability has a “significant” impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

“Risk” vs. “Critical”

**RISK:**
Evaluate the likelihood a PP is critical by conducting studies to determine if PP does or does not have an effect on CQA’s

**CRITICAL:**
Knowledge/data confirms CQA is affected by PP

Requires some level of control
Risk Assessment

It is neither always appropriate nor always necessary to use a formal risk management process..... The use of informal risk management processes can also be considered acceptable. -ICH Q9

- Documented prior knowledge & apply sound scientific principles
- Tools - FMEA, Fishbone, Databases
  - Standardization / knowledge base for attributes & parameters
- Justification

<table>
<thead>
<tr>
<th>Drug Product CQA's</th>
<th>Variables &amp; Unit Operations</th>
<th>ER beads – drug layering</th>
<th>ER coating</th>
<th>Final blending</th>
<th>Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td></td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td>High</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Degradation Products</td>
<td></td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>CU</td>
<td></td>
<td>Medium</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Drug Release</td>
<td></td>
<td>Medium</td>
<td>High</td>
<td>Medium</td>
<td>High</td>
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</tbody>
</table>
Risk Assessment of the Drug Substance, Material Attributes, Formulation Variables, and Processing Parameters:

Risk identification through risk assessment process

Risk mitigation through structured experimental studies → control strategy (OFAT, DOE’s, etc.,)

Documenting residual risk, if any, through appropriate justification
# How Perrigo Brings QbD into Development

## Example of Process Mapping for Risk Assessment of Process Parameters

<table>
<thead>
<tr>
<th>Process Parameters</th>
<th>Type* (C/UC)</th>
<th>In-Process Quality Attributes</th>
<th>Outputs (&quot;X&quot;) Drug Product CQAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Mix</td>
<td>Speed</td>
<td></td>
<td>Assay, Content Uniformity, Dissolution</td>
</tr>
<tr>
<td></td>
<td>Screen Size and Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amperage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setup</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feed Rate and Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loading Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Knife Setup</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### In-Process Quality Attributes
- Particle Size Distribution
- Bulk Density
- Tap Density
- Yield & Accountability
- Appearance

### Drug Product – Critical Quality Attributes
- Assay
- Content Uniformity
- Dissolution

### Process Parameters Inputs
- Speed
- Screen Size and Type
- Amperage
- Setup
- Model
- Feed Rate and Type
- Loading Type
- Knife Setup

### Milling Fitzmill

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<tr>
<th>Process Parameters</th>
<th>Type* (C/UC)</th>
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<tr>
<td>Milling Fitzmill</td>
<td>Speed</td>
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| In-Process Quality Attributes
- Particle Size Distribution
- Bulk Density
- Tap Density
- Yield & Accountability
- Appearance

### Notes
- Process Mapping
- Risk Assessment Tool
**Critical Process Parameters (CPPs)**

<table>
<thead>
<tr>
<th>Formulation Processing Stage:</th>
<th>Drug Layering: Solution mixer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Parameter</td>
<td>Is this Critical?</td>
</tr>
</tbody>
</table>

**Critical Material Attributes (CMAs)**

<table>
<thead>
<tr>
<th>Material:</th>
<th>API</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material Attribute</td>
<td>Is this Critical?</td>
</tr>
</tbody>
</table>

**Identification of Critical Processing Parameters**

**Identification of Critical Material Attributes**
**Selection of Final Formula & Process and finalization of the control strategy**

<table>
<thead>
<tr>
<th>Drug Product CQA</th>
<th>Incoming materials</th>
<th>Process parameter controls</th>
<th>In-process controls (measurements)</th>
<th>Release Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>ID testing on drug substance</td>
<td>None</td>
<td>None</td>
<td>Tested at release</td>
</tr>
<tr>
<td>Assay</td>
<td>Drug substance purity</td>
<td>Blend Time Press Speed</td>
<td>In-process core tablet assay measured by NIR</td>
<td>None</td>
</tr>
</tbody>
</table>

Case Study
Identified CQAs for the DR beads based upon prior knowledge and RLD

- Assay
- CU
- Drug Release (Acid & Buffer Stage)
- Impurities
Risk Assessment & Risk Mitigation for Enteric Coating Stage

**Initial Risk Assessment**

<table>
<thead>
<tr>
<th>CQA: Acid Stage Dissolution</th>
<th>Input Process Parameters</th>
<th>Risk</th>
<th>Justification and Initial Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coating Load Size</td>
<td>Low</td>
<td>Based upon scientific literature and/or documented prior knowledge</td>
</tr>
<tr>
<td></td>
<td>Atomization Air Pressure</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spray (Flow) Rate</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Product Temperature</td>
<td>Medium</td>
<td></td>
</tr>
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**Risk Mitigation Study:**

- Fluid Bed Coating Process via GPCG 30 (Glatt fluid bed system)
- Choose optimized DOE to evaluate impact of process parameters factors and selected ranges upon CQAs
DOE Study (EC Beads)

**Inputs:**
- Product Temperature
- Spray Rate

**Responses:**
- Drug Release (acid resistance)

**Outcome**

The contour plot provides the relationship of drug release to the product temperature and spray rate inputs resulting in the ability to have a control strategy.
### Risk Mitigation for Enteric Coating Stage

#### Before Studies

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<th>CQA:</th>
<th>Acid Stage Dissolution</th>
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#### After Studies

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<td>Spray (Flow) Rate</td>
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<td>Product Temperature</td>
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Risks mitigated through process understanding and control strategy
## Identification of Critical Process Parameters

<table>
<thead>
<tr>
<th>Process Parameter</th>
<th>Is this Critical?</th>
<th>Range</th>
<th>Type of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomization Air Pressure</td>
<td>No</td>
<td>See Batch Record</td>
<td>Operating Range</td>
</tr>
<tr>
<td>Spray (Flow) Rate</td>
<td>Yes</td>
<td>See Batch Record</td>
<td>In-Process Control</td>
</tr>
<tr>
<td>Coating Load Size</td>
<td>No</td>
<td>See Batch Record</td>
<td>Fixed</td>
</tr>
<tr>
<td>Product Temperature</td>
<td>Yes</td>
<td>See Batch Record</td>
<td>In-Process Control</td>
</tr>
</tbody>
</table>
Technology Transfer to Commercial Scale Enteric Coating Process

“Scale-Out” Batch size increase 10 X

Pilot Scale
Glatt GPCG 30

Commercial Scale
Glatt GPCG 500
1. Apply scale-up factors based upon
   - Literature
   - Equipment Manufacturers Recommendations
   - Prior Knowledge

   **Pilot Scale**
   Glatt GPCG 30
   Single Wurster Insert

   **Commercial Scale**
   Glatt GPCG 500
   Six Wurster Inserts

2. Verify CPP control strategy via augmented DOE at commercial scale
   - Design space verified at target and min/max of ranges identified at pilot scale
Case Study Conclusion

- Systematic process parameter risk assessment followed
- Structured experimental study completed to ensure process understanding
- Risk mitigation of CPPs achieved via control strategy
- Successful process scale-up by utilizing scale-up factors
- Verified CPPs from pilot scale studies

Robust Process is Established at Commercial Scale
QbD-Recap

**Structure**
- Disciplined Development Approaches
  - Risk Assessment Driven Development
    - Focus on CQAs

**Technology**
- Experimental Planning & Design
- Analytical Technologies (ex. High-Throughput screening)
- Data Management

**Knowledge**
- Increased Understanding
  - Materials
  - Process Parameters
- Multivariate Studies linking materials & processes

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QbD-Recap

Disciplined Development Approaches

Risk Assessment Driven Development - Focus on CQAs

Structure

- Experimental Planning & Design
- Analytical Technologies (ex. High-Throughput screening)
- Data Management

Technology

- Increased Understanding
  - Materials
  - Process Parameters

Knowledge

- Efficient, Robust and Controlled Product to Commercial Market

Efficient, Robust and Controlled Product to Commercial Market
Acknowledgements

Raj Thota, Director, CHC Formulation Research & Development

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