QbD & QRM Strategies in Pharmaceutical Product Development

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American Association of Pharmaceutical Scientists
Southern California Pharmaceutical Discussion Group (SCPDG)
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ICH Q8-Q9-Q10: Big Picture

Pharmaceutical Development: Quality by Design Q8 + Quality Risk Management Q9 + Modern Effective Pharmaceutical Quality Systems Q10

Lower Risk Operations
Innovation and Continual Improvement
Optimized Change Management Process
Flexible Regulatory Approaches
To design a quality product and its manufacturing process to deliver the intended performance of the product.
To create an acceptable dosage form, all the inputs must be considered. Some inputs may be more important than others for individual projects.
Quality by Design

QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management.

**Overall Principle of this approach:**

Quality cannot be tested into products; i.e., Quality should be built in by design.
Key Principles of QbD

• Systematic approach to
  – Product design
  – Process design & control
  – Process performance & continuous improvement

• Quality: Quality cannot be tested in the product; it should be built in by design

• Product Knowledge: Scientific understanding in the establishment of design, specifications and manufacturing

• Regulatory Flexibility
  – Design space proposed by applicant is subject to regulatory assessment and working within the space is not a change
  – Movement out of design space is considered to be a change and requires post-approval change process
**QbD Workflow**

1. Labeled Use Safety and Efficacy
2. DEFINE Quality Target Product Profile
3. DESIGN Formulation and Process
4. IDENTIFY Critical Material Attributes and Critical Process Parameters
5. CONTROL Materials and Process

TARGET → DESIGN → IMPLEMENTATION

Adapted from L. Yu, FDA.
7-Step QbD Process for Pharmaceutical Product Development

1. Quality target product profile
2. Identify approach to drug product formulation/manufacturing process.
3. Identify potential Critical Quality Attributes of RM/DS/DP
4. Identify potential Critical Process Parameters
5. Using risk assessment & experimental approaches, determine the functional relationships that link raw material CQAs and unit operation CPPs to drug product CQAs
6. Refine formulation and manufacturing process, if necessary and repeat steps 3 -5 to meet QTPP defined in Step 1.
7. Establish Design Space and Control Strategy
# QTPP for a Sterile Preserved Solution (Phase 3 Development)

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Target</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage form</strong></td>
<td>Sterile Solution</td>
<td>Sterile Suspension</td>
</tr>
<tr>
<td><strong>Dose Strengths</strong></td>
<td>0.1 - 0.15 % w/v</td>
<td>NLT 0.075% w/v</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>6.8-7.4</td>
<td>6.0-7.8</td>
</tr>
<tr>
<td><strong>Preservative(^1)</strong></td>
<td>NMT 50 ppm</td>
<td>NMT 100 ppm</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Once-a-day</td>
<td>Once-a-day (BID is acceptable if efficacy better than current product)</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>NLT 18 months at Room Temperature</td>
<td>Refrigerated until dispensed (60 days RT storage)</td>
</tr>
<tr>
<td><strong>Primary Packaging</strong></td>
<td>Bottles</td>
<td>Bottles</td>
</tr>
</tbody>
</table>
| **Secondary Packaging**| Cardboard Carton              | Cardboard Carton                                  
|                        |                               | No new inks for labels                            |

\(^1\)Needs to meet US & EU criteria for APET

For Devices – PRD (ISO 13485)
Derived from Phase 3 QTPP if Stage-Gate approach is chosen

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Acceptable Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Solution or Suspension</td>
</tr>
<tr>
<td>Dose Strengths</td>
<td>0.05 – 0.2% w/v</td>
</tr>
<tr>
<td>Number of dose Strengths</td>
<td>NMT 3 strengths for Phase 1</td>
</tr>
<tr>
<td>pH</td>
<td>5.5-7.8</td>
</tr>
<tr>
<td>Preservative(^1)</td>
<td>Preservative-free</td>
</tr>
<tr>
<td>Storage</td>
<td>Refrigerated until dispensed</td>
</tr>
<tr>
<td></td>
<td>(60 days RT storage)</td>
</tr>
<tr>
<td>Primary Packaging</td>
<td>Unit of use in Plastic Bottles</td>
</tr>
</tbody>
</table>
7-Step QbD Process for Pharmaceutical Product Development

1. Quality target product profile
2. Identify approach to drug product formulation/manufacturing process.
3. Identify potential Critical Quality Attributes of RM/DS/DP
4. Identify potential Critical Process Parameters
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7. Establish Design Space and Control Strategy
Product Devt Strategy is heavily driven by the maturity of the enabling technology.

**Exploration:**
Existing Knowledge not sufficient to solve the problem identified. New knowledge needs to be created and acquired to contribute to the existing body of knowledge.

**Exploitation:**
Utilization of existing knowledge for innovative problem solving.

Revilla, E., Rodriguez, B., 2011
Technovation (31) 118-127
Dosage Form & Drug Delivery Route (Enabling Formulation Technology)

- The level of knowledge exploration (vs. exploitation) could increase as the QTPP goes from eye drops to intravitreal injections/biodegradable implants.
- The product development strategy will be driven partly by organization’s domain expertise with these types of dosage forms.

Product Development – Key CMC Milestones

1. Drug Substance Solid State Form Recommendation
2. Drug Substance Synthetic Process (Early Devt, Phase3, Commercial)
3. Formulation Recommendation (GLP, Early Devt, Phase3, Commercial)
4. Analytical Methods & Specifications (Phase Appropriate)
5. Drug Product Recommendation (Commercial Product Definition)
6. Commercial DP Manufacturing Process Recommendation
7. Process Validation (DS & DP)
Regulatory Considerations

- **Exploratory IND Approach**
- **Bridging Strategy**
  - Availability of Preclinical/Invitro Models to assess formulation equivalence
  - GLP Tox Studies
  - Bioequivalence Studies
  - Biomarker availability/Ease of assessing clinical efficacy/safety
- **Global Product vs Specific Region**
  - Color (or Colour)
  - Preservative
  - Dosage Form size
  - COGs
- **Orphan Drug:** <200,000 people (US), NMT 5 in 10,000 people (EU)
Begin With the End in Mind

• **DRUG SUBSTANCE (NAME, MANUFACTURER)**
  – General Information (name, manufacturer)
  – Manufacture (name, manufacturer)
  – Characterisation (name, manufacturer)
  – Control of Drug Substance (name, manufacturer)
  – Reference Standards or Materials (name, manufacturer)
  – Container Closure System (name, manufacturer)
  – Stability (name, manufacturer)

• **DRUG PRODUCT (NAME, DOSAGE FORM)**
  – Description and Composition of the Drug Product (name, dosage form)
  – Pharmaceutical Development (name, dosage form)
  – Manufacture (name, dosage form)
  – Control of Excipients (name, dosage form)
  – Control of Drug Product (name, dosage form)
  – Reference Standards or Materials (name, dosage form)
  – Container Closure System (name, dosage form)
  – Stability (name, dosage form)

• Facilities and Equipment (name, manufacturer)

ICH Quality Guidelines: Key Information for Registration
7-Step QbD Process for Pharmaceutical Product Development

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CQAs and CPPs

• Critical Quality Attribute (CQA)
  – A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
  – API Particle Size, Purity, drug release, stability, sterility……

• Critical Process Parameter
  – A process parameter, e.g. temp, time, speed, when variable it can affect the CQA of a product or process
  – Critical Process Parameters (CPP) identified using a risk analysis investigated extensively using a DOE.

• Non-Critical Process Parameters
  – A process parameter identified as low risk which leads to low probability of product failure
CQAs for a Sterile Ophthalmic Solution (Example)

<table>
<thead>
<tr>
<th>Critical Quality Attribute</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Solution</td>
</tr>
<tr>
<td>Potency (Strength)</td>
<td>0.05-0.1 %</td>
</tr>
<tr>
<td>Appearance</td>
<td>Clear and colorless, no visible particulates</td>
</tr>
<tr>
<td>Identity</td>
<td>Positive for Compound X</td>
</tr>
<tr>
<td>Assay</td>
<td>95 – 105% at release 90-110% at end of shelf</td>
</tr>
<tr>
<td>Impurities</td>
<td>No single impurity greater than 0.9%</td>
</tr>
<tr>
<td>pH</td>
<td>Physiological pH</td>
</tr>
<tr>
<td>Isotonicity</td>
<td>280-330 mOsm</td>
</tr>
<tr>
<td>APET</td>
<td>Meet USP and PhEur A criteria</td>
</tr>
<tr>
<td>Sterility</td>
<td>Meet USP and PhEur</td>
</tr>
<tr>
<td>Particulate Matter</td>
<td>Meet USP and PhEur</td>
</tr>
<tr>
<td>Leachables</td>
<td>Below safety threshold</td>
</tr>
</tbody>
</table>
Sample CQAs for a Biodegradable Polymer

<table>
<thead>
<tr>
<th>Critical Quality Attribute</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual Monomer</td>
<td>Less than 0.2% w/w</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>15k to 20k</td>
</tr>
<tr>
<td>Bulk Density, g/mL</td>
<td>0.4 to 0.8</td>
</tr>
<tr>
<td>Crystallinity</td>
<td>X-ray amorphous</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Less than 0.5EU/mg</td>
</tr>
</tbody>
</table>
Sample CPPs for a Mixing Unit Operation

1. Mixing Time
2. Mixing Speed
3. Process Temperature
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Typical Risk Management Process

1. What can go wrong?
2. What is the likelihood that it will go wrong?
3. What would be the consequences?

1. Above risk at an acceptable level?
2. What can be done to reduce or eliminate risks?
3. Balance between Benefits, Risks and Resources?
4. Any new risks introduced?
Risk Assessment – General Framework

Quality Target Product Profile
 Drug substance properties; prior knowledge
 Proposed formulation and manufacturing process

Determination of Cause – Effect relationships
 (Risk Identification with subsequent Risk Analysis)

Risk-based classification
 (Risk Evaluation)

Parameters to investigate (e.g. by DOE)
 (Risk Reduction 1. proposal; 2. verified)

Product and process characteristics on the final drug product

Control strategy

Formulation Design Space

Process Design Space by Unit Operation

EFPIA Team, P2 Mock Doc
## Simple Risk Assessment (Example)

<table>
<thead>
<tr>
<th>Quality Attribute of DS, DP, Excipient, or Unit Operation CPP</th>
<th>Potential Risk</th>
<th>Probability of Occurrence (Lo, Med, Hi)</th>
<th>Potential Impact to Quality</th>
<th>Risk Reduction / Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS Solid State Form</td>
<td>New polymorph of DS formed</td>
<td>Med</td>
<td>More complex formulation needed if dose strength is above XX%.</td>
<td>Develop a back-up formulation</td>
</tr>
<tr>
<td>DS Impurity</td>
<td>New Impurity generated during process optimization</td>
<td>Lo</td>
<td>Qualification of new impurity</td>
<td>Perform process optimization earlier in development (or) plan for a potential tox study later in development</td>
</tr>
<tr>
<td>DP Impurity</td>
<td>Product degrades during room temperature storage</td>
<td>Hi</td>
<td>Reduced product Shelf-life</td>
<td>Refrigerate product until dispensed to patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Develop back-up formulations</td>
</tr>
</tbody>
</table>
Fishbone Diagram

Solvent Systems
- Ionic Strength (API, reaction products)
- Sodium vs Ammonium Salts
- Solvent Polarity
- Acetic Acid: Ethanol
- Water

Batch Size
- Tank Design
- Impeller Speed
- Impeller Design

Incoming Materials
- Raw Materials Organic Impurities
- Raw Materials Inorganic Impurities
- Incoming Intermediate Impurities
- API Charge/Concentration

Reactor Conditions
- Temperature
- Time of Crystallization
- Distillation Rate
- Seed Amount/morphology
- Seeding Time
- Seeding pH
- d[pH]/dt

Crystal Form

From J-M. Geoffroy, Takeda
Risk Assessment using FMEA

<table>
<thead>
<tr>
<th>CQA or CPP</th>
<th>Potential Failure Mode</th>
<th>Potential Effects of Failure</th>
<th>Severity</th>
<th>Likelihood</th>
<th>Controls</th>
<th>Detachability</th>
<th>RPN</th>
<th>Recommended Actions</th>
<th>Responsibility &amp; Target Completion Dates</th>
<th>Actions Taken</th>
<th>New Severity</th>
<th>New Likelihood</th>
<th>New Detachability</th>
<th>New RPN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Write down each failure mode & potential consequences of failure
- Write down the potential cause(s) and rate the likelihood of each failure
- RPN (Risk Priority Number) = Severity x Likelihood x Detectability
- Rate the severity of each failure. A 1 to 10 scale may be used or a 1, 3, 9 scale may be useful to separate out close effects. Use the same scale for likelihood & detectability.
- Examine the current formula/process and rate the detectability of each failure
### CQA – Unit Operation Relationship (Example)

<table>
<thead>
<tr>
<th>DP CQA Unit Operation</th>
<th>Order of addition</th>
<th>Mixing</th>
<th>pH adjust</th>
<th>Filtration</th>
<th>Filling</th>
<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Med</td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Assay</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Impurity</td>
<td>Low</td>
<td>Med</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>pH</td>
<td>Low</td>
<td>Low</td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Tonicity</td>
<td>Low</td>
<td>Med</td>
<td>High</td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>BAK</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sterility</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
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You CANNOT have a constant output from a fixed process and variable input

From K. Morris, U. Hawaii - Adapted from Rick Cooley, Eli Lilly, and Jon Clark CDER-FDA
Conceptual Representation of Knowledge, Design and Control Spaces

- Specifications
- Continuous Improvement without Regulatory Approval

Some Definitions

- **Design Space**
  - **Clinical Relevance**
  - Multi-dimensional space that encompasses combinations of product design, manufacturing process design, critical manufacturing process parameters and component attributes that provide assurance of suitable product quality and performance

- **Control Space**
  - **Process Capability**
  - Multi-dimensional space that encompasses process operating parameters and component quality measurements that assure process or product quality. It is a subset of the design space

- **Control Strategy**
  - **Change Control, Continuous Improvement, Regulatory Considerations**
  - Strategy/Methodology to mitigate risks associated with the batch when the critical and non-critical process parameters fall outside the control space but within the design space
  - A control strategy is designed to ensure that a product of required quality will be produced consistently
## Design Space: Formulation and Mixing Unit Operation (Example)

<table>
<thead>
<tr>
<th><strong>Formulation Ingredients (or)</strong> Unit Operation CPP</th>
<th><strong>Design Space</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubilizer Concentration</td>
<td>0.5% to 1.0% w/v</td>
</tr>
<tr>
<td>Viscosity Agent Concentration</td>
<td>1% to 2% w/v</td>
</tr>
<tr>
<td>Drug Substance Concentration</td>
<td>98% to 102%</td>
</tr>
<tr>
<td>Buffer Concentration</td>
<td>+/- 10% of target</td>
</tr>
<tr>
<td>Tonicity Agent</td>
<td>+/- 10% of target</td>
</tr>
<tr>
<td>Mixing Time</td>
<td>30 min to 120 min</td>
</tr>
<tr>
<td>Mixing Speed</td>
<td>100 rpm to 200 rpm</td>
</tr>
<tr>
<td>Temperature</td>
<td>NMT 50 °C</td>
</tr>
</tbody>
</table>
7-Step QbD Process for Pharmaceutical Product Development

1. Quality target product profile

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4. Identify potential Critical Process Parameters

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7. Establish Design Space and Control Strategy
Questions / Discussion
Control Strategy

• A control strategy is designed to ensure that a product of required quality will be produced consistently.

• A control strategy can include, but is not limited to, the following:
  – Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
  – Product specification(s);
  – Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
  – In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
  – A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.
Is QbD really a new concept?

- QbD is not a new concept from the technology perspective
- QbD is new relative to regulatory review and submission
- QbD is optional and should not become a regulatory requirement as agreed to in ICH Q8
- QbD will not necessarily be included in all submissions
- Generation of QbD information during IND phases should be at industry discretion