Quality by Design (QbD) for Topical Dermatologic Products

Andre S. Raw, Ph.D
Director - Division of Chemistry I
FDA-CDER-Office of Generic Drugs

andre.raw@fda.hhs.gov

*Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA
Quality by Design (QbD)

- ICH Q8(R2) Definition
  - a systematic approach to development
  - begins with predefined objectives
  - emphasizes product and process understanding and process control,
  - based on sound science and quality risk management

**Pharmaceutical Quality** = \( f \) (Drug substance, excipients, manufacturing, and packaging)
Overview of QbD

TARGET → DESIGN and UNDERSTANDING → IMPLEMENTATION

- **Labeled Use Safety and Efficacy**
- **Define Quality Target Product Profile**
- **Product Design and Understanding**
- **Process Design and Understanding**
- **Control Strategy**
- **Continual Improvement**

**Primary topics**:
- Define Quality
- Target Product Profile
- Process Design and Understanding
- Control Strategy
- Continual Improvement

**Secondary topics**:
- Labeled Use Safety and Efficacy
- Implementing QbD

#### TABLE 1  Typical Sites of Action and Dosage Forms for Various Topical Routes of Administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Site of action</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Local or systemic</td>
<td>Aerosols, Creams, Emulsions, Gels, irrigations, Lotions, Ointments, Strips, Pastes, Powders, Solutions, Tinctures, Suppositories, Suspensions, Transdermal systems</td>
</tr>
<tr>
<td>Ear (otic)</td>
<td>Local</td>
<td>Emulsions, Ointments, Solutions, Suspensions, Inhalations, Powders, Solutions, Suspensions, Inhalations</td>
</tr>
<tr>
<td>Nose (nasal)</td>
<td>Local or systemic</td>
<td>Aerosols (two-phase, three-phase, and foam)</td>
</tr>
<tr>
<td>Mouth--(oral respiratory)</td>
<td>Local or systemic</td>
<td></td>
</tr>
<tr>
<td>Anus (rectal)</td>
<td>Local or systemic</td>
<td></td>
</tr>
<tr>
<td>Vagina (vaginal)</td>
<td>Local</td>
<td>Emulsions, Ointments, Solutions, Suspensions, Strips</td>
</tr>
</tbody>
</table>

The Challenges

Generally we account for Formulation Differences to Ensure Equivalent Safety and Effectiveness via Comparative Pharmacodynamic Endpoint (Topical Steroids) or Clinical Endpoint (Most Other Topicals)

However

21 CFR 320.34 Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence.

![Graph of log[Dose] vs. Response with EC50 and EC90 highlighted.]

Often we are here
Paradigm Shift

Traditional Approach

- ANDA Formulation/Process Submitted Without Context
  
  Claimed to be Acceptable Based Upon a Passing BE study to the RLD
  
  "Equivalence by Testing"

QbD Approach

- QTPP/CQA: predefined target

  Asks Sponsors How They Systemically Arrived at a Pharmaceutical Equivalent & Bioequivalent Drug Product
  
  "Equivalence by Design"
QTPP for Generic Topical Products

- Analysis of the reference listed drug (RLD) product
  - RLD labeling
    - Dosage form, Strength, Route of administration
    - Clinical Pharmacology
    - Indication and Usage
    - Precautions/ Adverse Reactions
    - Dosage and Administration
    - How supplied (container closure system and storage)
  - Comprehensive testing
    - Physical Attributes: appearance, color, odor, pH, rheological behavior (consistency, viscosity), drug particle size, oil globule size, spreadability etc.
    - Identification of inactive ingredients including preservative and antioxidant etc.
    - Assay, homogeneity, and tube uniformity
    - Impurity profile: RLD near expiration
    - In Vitro Release Test (Flux assay using porcine ear/synthetic membrane/cadaver skin)

- Other resources
  - Scientific literature/Patents
  - FOI requests
  - FDA database for dissolution / bioequivalence recommendation

- Begin with the end in mind: pharmaceutical equivalence and bioequivalence
### Example Quality Target Product Profile (QTPP) for X Cream USP, N%

<table>
<thead>
<tr>
<th>QTPP Element</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Cream</td>
<td>Pharmaceutical equivalence requirement: Same dosage form</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Topical</td>
<td>Pharmaceutical equivalence requirement: Same route administration</td>
</tr>
<tr>
<td>Dosage strength</td>
<td>N% w/w</td>
<td>Pharmaceutical equivalence requirement: Same strength</td>
</tr>
<tr>
<td>Stability</td>
<td>At least 24-month shelf-life at room temperature</td>
<td>Equivalent to or better than RLD shelf-life, pharmaceutical equivalence requirement.</td>
</tr>
<tr>
<td>Drug product quality attributes</td>
<td>Physical Attributes: rheological behavior, drug particle size, oil globule size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Identification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assay</td>
<td>Pharmaceutical equivalence requirement: Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality)</td>
</tr>
<tr>
<td></td>
<td>Homogeneity and Tube Uniformity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Degradation products/Residual Solvent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preservatives Content</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microbial Limits</td>
<td></td>
</tr>
<tr>
<td>Container closure system</td>
<td>Identical primary packaging to RLD</td>
<td>Match RLD and for patient acceptability</td>
</tr>
<tr>
<td>Package Integrity</td>
<td>No failure</td>
<td>Needed for stability, clinical effectiveness and safety</td>
</tr>
<tr>
<td>Administration</td>
<td>Concurrence with RLD labeling</td>
<td>Information provided in the RLD labeling</td>
</tr>
</tbody>
</table>
## Example Critical Quality Attributes (CQA) for X Cream USP, N%  

<table>
<thead>
<tr>
<th>CQA</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Positive for Active</td>
<td>Needed for clinical effectiveness</td>
</tr>
<tr>
<td>Assay</td>
<td>90 – 110%</td>
<td>Needed for clinical effectiveness</td>
</tr>
<tr>
<td>Impurities</td>
<td>Impurity A: NMT 0.2%</td>
<td>Needed for safety</td>
</tr>
<tr>
<td></td>
<td>Impurity B: NMT 0.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any individual unknown: NMT 0.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Impurities: NMT 0.5%</td>
<td></td>
</tr>
<tr>
<td>Homogeneity and Tube Uniformity</td>
<td>Top, middle and bottom of three containers, nine assay values should be within 90.0% to 110.0% label claim and RSD is not more than 5%</td>
<td>Needed for clinical effectiveness</td>
</tr>
<tr>
<td>Physical Attributes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheological behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>particle size</td>
<td>Match RLD</td>
<td>Needed for clinical effectiveness and patient acceptability</td>
</tr>
<tr>
<td>Oil globule size</td>
<td></td>
<td>To demonstrate similar arrangement of matter to RLD (Q3)</td>
</tr>
<tr>
<td>In Vitro Release Test</td>
<td>Match RLD</td>
<td>In-vitro Surrogate used to guide BE</td>
</tr>
<tr>
<td>Microbial Limits</td>
<td>Meet USP &lt;61&gt;</td>
<td>Needed for safety</td>
</tr>
<tr>
<td>Residual Solvents*</td>
<td>Meet USP &lt;467&gt;</td>
<td>Needed for safety</td>
</tr>
</tbody>
</table>
## Implications of QTPP Design Target

<table>
<thead>
<tr>
<th>Generic</th>
<th>RLD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredient</strong></td>
<td><strong>Amount % w/w</strong></td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>1.0</td>
</tr>
<tr>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Excipient B</td>
<td>20.0</td>
</tr>
<tr>
<td>Excipient C</td>
<td>1.9</td>
</tr>
<tr>
<td>Excipient D</td>
<td>1.1</td>
</tr>
<tr>
<td>Preservative A</td>
<td>1.0</td>
</tr>
<tr>
<td>Purified Water, USP</td>
<td>72</td>
</tr>
</tbody>
</table>

**Dichotomy:** The RLD uses excipient A which are “purported” to have functionality (e.g. retentive properties on the epidermis) and the generic uses excipients C/D which have no evidence of retentive properties. With these formulation differences, how can we ensure equivalent effectiveness, given the insensitivity of clinical BE studies?
Understanding how the sponsor systematically arrived in their development program at their formulation based upon in vitro flux studies in skin to mimic those of excipient A would be informative toward ensuring equivalence.

Sponsors are strongly encouraged to provide this development information in the context of their QTPP/CQA to avoid more questions from the FDA regarding their formulation design.
Active ingredient:  Tretinoin (NDA 020475)
Form/Route:  Gel/Topical

Pharmaceutical Equivalence:

If a proposed generic drug product does not use microsphere technology, or if the formulation contains microspheres that are substantially different from that of the reference listed drug (RLD), then a drug stability test in presence of benzoyl peroxide (BPO) and UV light exposure and a comparative in vitro release test should be performed to support pharmaceutical equivalence. We recommend you conduct the in vitro release test using a diffusion cell system with excised human skin, a non-occlusive system in the donor cell, a finite dosing technique, and aqueous media at physiological pH in the receptor cell. The model should be adequately validated. We recommend…
Product & Process Understanding

**STEP 1**
Identify all possible material attributes and process parameters

**STEP 2**
Identify high risk attributes or parameters based on risk assessment and scientific knowledge

**STEP 3**
Identify levels or ranges of these high risk attributes or parameters

**STEP 4**
Design and conduct experiments, using DOE when appropriate

**STEP 5**
Analyze the experimental data

**STEP 6**
Develop a control strategy

Continuous Improvement
Product Understanding

Past/Present Paradigm

Single Batch Manufacturable at Exhibit (Biobatch) Scale and Placed on Stability

Does this Ensure Sponsor has Developed a Robust Formulation and with Adequate Stability Characteristics?

Has Sponsor Identified Critical Attributers of Active or Excipients that Need Control???

QbD Paradigm

Risk Assessment

Identification of Active/Excipient Attributes Having High Likelihood to Affect DP CQAs

Experimentation (as Needed) To Determine Impact on Active/Excipient Attributes On Drug Product CQAs

Adoption of a Control Strategy on Active/Excipients CMA’s To Mitigate Risk of CQA failures
## Risk Assessment for Formulation Component

<table>
<thead>
<tr>
<th>Formulation Component</th>
<th>Potential Risk</th>
<th>Potential Impact on Drug Product CQAs</th>
<th>Action Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>Particle size or morphology change</td>
<td>Shift in content uniformity, drug release and dermal distribution of the drug</td>
<td>Micronized drug substance with identical solid state form to the RLD from a qualified source is used for the drug product manufacturing and particle size is measured as part of drug substance release testing with a tight limit of D90 of not more than 10 µm. Drug concentration in the cream preparation needs to be monitored to ensure homogeneity of drug distribution in the drug product matrix.</td>
</tr>
<tr>
<td>White Petrolatum</td>
<td>Viscosity variation</td>
<td>Shift in viscosity</td>
<td>White petrolatum from a qualified source is used for the drug product manufacturing. Consistency is measured as part of every white petrolatum lot via release testing using more stringent limits than USP limits to ensure product viscosity closely matching that of the RLD.</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>Unidentified</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Methyl and Propyl Paraben</td>
<td>Possible chemical instability of preservatives in the cream</td>
<td>Shift in preservative content in the cream</td>
<td>The antimicrobial properties of the drug product are studied during the product development stage through antimicrobial effectiveness test. Based on the results from these microbial studies, set an adequate lower limit of preservative content for drug product release and stability specifications to reduce the risk of microbial contamination.</td>
</tr>
<tr>
<td>Purified Water</td>
<td>Increased water activity and bacteria growth potential</td>
<td>Drug Product Microbial limit</td>
<td>Quality system, cGMP</td>
</tr>
</tbody>
</table>
An Example: Excipient CMA Identification and Control

• $2^2$ factorial design is used to investigate the effect of acid value variation for two excipients (cetyl ester wax and glyceryl monostearate) used in a cream formulation on chemical stability of a drug

• % impurity A detected for stability samples stored at 40°C/75% RH for six months as the response
**Process Optimization**

### Past/Present Paradigm

- Exhibit (Biobatch) Production Record
- No Data to Classify CPPs versus non-CPPs
- 10 x Scale-Up
  - Same Equipment/Operating Principle
- Full Production Batches (Not Reviewed by OGD)

### QbD Paradigm

- Risk Assessment
  + Design of Experiments
- Classify CPPs versus non-CPPs in the unit Operation
- Define Design Process Space for CPPs at Pilot Scale (Bioequivalence Batch)
- Increased Likelihood of a Successful Commercial-Scale Process

**Can Sponsor Reliably Manufacture at Commercial Production Scale (or Even at the Same Scale)_ABCDEFGH?
Manufacturing Process Development Example

• A proposed manufacturing process calls for the emulsification of aqueous and oil phases to form a cream base and subsequent dispersion of the drug substance into the cream base through powder eduction.
### Example Initial Risk Assessment for Process Development

<table>
<thead>
<tr>
<th>Drug Product CQA</th>
<th>Manufacturing Operation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharmacy</td>
<td>Aqueous Phase</td>
</tr>
<tr>
<td>Appearance</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Assay</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Impurities</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Content Uniformity</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Drug Particle Size</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Potentially High Risk Process Variables

• Powder Eduction Rate
• Rotor Speed
• Rotor/Stator Gap
• Mixing time
• Mixing Speed
• Homogenization time
Screening DOE to Identify Critical Process Parameters

- Following the initial risk assessment, a screening design experiment is used to evaluate the relative importance of the process variables.

- Screening DOE options
  - Plackett-Burman designs
  - Fractional factorial designs (Resolution III or IV)
  - Taguchi orthogonal arrays
Parameter Estimates and Half-Normal Plot for 12-run Plackett-Burman Design Generated by JMP-9 Software Tool (Response: %RSD)

### Parameter Estimates

| Term                          | Estimate | Std Error | t Ratio | Prob>|t| | Lower 95%   | Upper 95%   |
|-------------------------------|----------|-----------|---------|--------|-------------|-------------|
| Intercept                     | 4.875    | 0.18246   | 26.72   | <.0001 *| 4.4059715   | 5.3440285   |
| Mixer Speed(100,300)          | -0.041667| 0.18246   | -0.23   | 0.8284 | -0.510695   | 0.4273618   |
| Mixing Time(10,20)            | -0.208333| 0.18246   | -1.14   | 0.3053 | -0.677362   | 0.2606951   |
| Rotor/Stator Gap(10,18)       | -0.358333| 0.18246   | -1.96   | 0.1068 | -0.827362   | 0.1106951   |
| Powder Eduction Rate          | 0.908333 | 0.18246   | 4.98    | 0.0042 *| 0.4393049   | 1.3773618   |
| Rotor Speed(1000,2000)        | 0.641667 | 0.18246   | 3.52    | 0.0170 *| 0.1726382   | 1.1106951   |
| Homogenization Time(10,30)    | -1.158333| 0.18246   | -6.35   | 0.0014 *| -1.627362   | -0.689305   |

### Sorted Parameter Estimates

| Term                          | Estimate | Std Error | t Ratio | Prob>|t| |
|-------------------------------|----------|-----------|---------|--------|-----|
| Homogenization Time(10,30)    | -1.158333| 0.18246   | -6.35   | 0.0014 *|     |
| Powder Eduction Rate          | 0.908333 | 0.18246   | 4.98    | 0.0042 *|     |
| Rotor Speed(1000,2000)        | 0.641667 | 0.18246   | 3.52    | 0.0170 *|     |
| Rotor/Stator Gap(10,18)       | -0.358333| 0.18246   | -1.96   | 0.1068 |     |
| Mixing Time(10,20)            | -0.208333| 0.18246   | -1.14   | 0.3053 |     |
| Mixer Speed(100,300)          | -0.041667| 0.18246   | -0.23   | 0.8284 |     |
Response Surface Designs for Process Optimization

• A response surface DOE is used to further optimize the identified significant process variables from screening DOE experiments.

• Response Surface Designs
  – Central composite design
  – Box-Behnken design
  – 3-level full factorial design
Central Composite Design for Investigating Three Process Variables to Minimize %RSD

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Homogenization Time (X₁)</th>
<th>Powder Eduction Rate (X₂)</th>
<th>Rotor Speed (X₃)</th>
<th>% RSD (Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+++</td>
<td>30</td>
<td>-1</td>
<td>1000</td>
</tr>
<tr>
<td>2</td>
<td>000</td>
<td>20</td>
<td>0</td>
<td>1500</td>
</tr>
<tr>
<td>3</td>
<td>a00</td>
<td>10</td>
<td>0</td>
<td>1500</td>
</tr>
<tr>
<td>4</td>
<td>+++</td>
<td>30</td>
<td>-1</td>
<td>2000</td>
</tr>
<tr>
<td>5</td>
<td>0A0</td>
<td>20</td>
<td>1</td>
<td>1500</td>
</tr>
<tr>
<td>6</td>
<td>00a</td>
<td>20</td>
<td>0</td>
<td>1000</td>
</tr>
<tr>
<td>7</td>
<td>--+</td>
<td>10</td>
<td>1</td>
<td>2000</td>
</tr>
<tr>
<td>8</td>
<td>---</td>
<td>10</td>
<td>-1</td>
<td>1000</td>
</tr>
<tr>
<td>9</td>
<td>000</td>
<td>20</td>
<td>0</td>
<td>1500</td>
</tr>
<tr>
<td>10</td>
<td>---</td>
<td>10</td>
<td>-1</td>
<td>2000</td>
</tr>
<tr>
<td>11</td>
<td>000</td>
<td>20</td>
<td>0</td>
<td>1500</td>
</tr>
<tr>
<td>12</td>
<td>00A</td>
<td>20</td>
<td>0</td>
<td>2000</td>
</tr>
<tr>
<td>13</td>
<td>+++</td>
<td>30</td>
<td>1</td>
<td>1000</td>
</tr>
<tr>
<td>14</td>
<td>0a0</td>
<td>20</td>
<td>-1</td>
<td>1500</td>
</tr>
<tr>
<td>15</td>
<td>--+</td>
<td>10</td>
<td>1</td>
<td>1000</td>
</tr>
<tr>
<td>16</td>
<td>+++</td>
<td>30</td>
<td>1</td>
<td>2000</td>
</tr>
<tr>
<td>17</td>
<td>A00</td>
<td>30</td>
<td>0</td>
<td>1500</td>
</tr>
</tbody>
</table>
Contour Plots of %RSD versus Powder Eduction Rate and Homogenization Time
Contour Plots of %RSD versus Rotor Speed and Homogenization Time
Contour Profiler

Contour Plots of %RSD versus Rotor Speed and Powder Eduction Time
Historical Paradigm for Scale-Up In ANDAs

10 x Scale-up Rule

ANDA Exhibit Batch

Commercial Batch

Is Commercial Scale Drug Product Equivalent to the ANDA Exhibit Batch (Is the arrangement of matter Q3 (e.g. emulsion droplet size, API particle size) the same as the pivotal ANDA Clinical Batch used to Establish Equivalence?)
Linkage of Commercial/Exhibit Batch Process Spaces

PAT Tools

Commercial Scale Product

Similar Arrangement of Matter between Clinical and Commercial Batches

Scale-up based upon underlying assumptions (similitude between different scales, empirical or semi-empirical models, etc)

Process Validation/Verification (Post-Submission) Confirm Points in Predicted Commercial Scale-Process Space
Summary

• The clearly predefined objectives (QTPP/CQA) is a powerful tool to guide formulation and process design and to keep the product development effort focused and efficient.

• Enhanced product and process understanding builds solid foundation for developing the Control Strategy
  – including identification of critical process parameters and critical attributes of excipients, drug substance, and/or container closure systems

• Implementation of the systematic science and risk-based approach will bring significant benefits to patient, industry and regulatory agency with the high quality drug products and manufacturing efficiencies.

• Risk assessment, DOE, Prior Knowledge etc. are useful tools for QbD implementation.
Acknowledgements

• Lawrence Yu
• Rong-Kun Chang
• Bing Cai
• Robert Lionberger
• Daniel (Yingxu) Peng
