Quality by Design, Revolution or Evolution?

Wim Oostra
1993
TU Delft

1998
Organon

2007
Schering-Plough

2009
MSD

2013
Abbott

And many more..
Content

• Introduction
• A bit of history
• Examples
  – A “New” product
  – Legacy product
• Today?
The Wall Street Journal: September 3rd 2003

New Prescription For Drug Makers: Update the Plants

"The Pharmaceutical Industry Has A Little Secret: Even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers."

"You need to improve" – Dr. McClellan lectured the industry..
The goal

Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach
A science and risk-based approach to product quality regulation incorporating an integrated quality systems approach

Introduction

FDA oversees the quality of drug products using a two-pronged approach involving review of information submitted in applications as well as inspection of manufacturing facilities for conformance to requirements for current Good Manufacturing Practice (cGMP). These two programs have served the country well by helping to ensure the quality of drug products available in the US. Now, as we approach the 25th anniversary of the last major revision to the drug cGMP regulations, it is time to step back and evaluate the currency of these programs so that:

- the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality;
- the latest scientific advances in pharmaceutical manufacturing and technology are encouraged;
- the submission review program and the inspection program operate in a coordinated and synergistic manner;
- regulation and manufacturing standards are applied consistently;
- management of the program encourages innovation in the pharmaceutical manufacturing sector; and
- FDA resources are used most effectively and efficiently to address the most significant health risks.
2006 view

Quality by Design

Product Specifications
- Desired clinical performance

Product Knowledge
- Doseage form, excipients
- Selection, stability, etc.

Process Design
- Unit operations, control strategy, etc.

Process Parameters
- Cpk, robustness, etc.

Process Performance
- Desired clinical performance

Product Specifications
- Desired clinical performance

Continuous Improvement

Moheb Nasr, March 29, 2006
Regulatory Flexibility: How?

- Quality by design
  - Structured product and process development
  - Process understanding and control capability
  - Design space

- Integration of prior knowledge and pharmaceutical development into C, M, C submission and review
  - Present the knowledge gained to provide a more comprehensive understanding of the product and manufacturing process for reviewers and inspectors
  - Risk based assessment and investigations and knowledge sharing (over a product’s life cycle)
Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Zip with all ICH Quality Guidelines in word format.

<table>
<thead>
<tr>
<th>Q1A - Q1E Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2 Analytical Validation</td>
</tr>
<tr>
<td>Q3A - Q3D Impurities</td>
</tr>
<tr>
<td>Q4 - Q4B Pharmacopoeias</td>
</tr>
<tr>
<td>Q5A - Q5E Quality of Biotechnological Products</td>
</tr>
<tr>
<td>Q6A - Q6B Specifications</td>
</tr>
<tr>
<td>Q7 Good Manufacturing Practice</td>
</tr>
<tr>
<td>Q8 Pharmaceutical Development</td>
</tr>
<tr>
<td>Q9 Quality Risk Management</td>
</tr>
<tr>
<td>Q10 Pharmaceutical Quality System</td>
</tr>
<tr>
<td>Q11 Development and Manufacture of Drug Substances</td>
</tr>
<tr>
<td>Q12 Lifecycle Management</td>
</tr>
<tr>
<td>Cross-cutting Topics</td>
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QbD Approach

Understand the Product

Understand the Process

Control the Process Over the Product Lifecycle
Elements of QbD

• QTPP
• Risk assessments (should be management)
• CQA’s
• CPP’s
• Control strategy (may include PAT)
• Design space
• Continuous improvement
## Development vs. operations

<table>
<thead>
<tr>
<th>Development</th>
<th>Commercial production</th>
</tr>
</thead>
<tbody>
<tr>
<td>One development site</td>
<td>Multi site operations</td>
</tr>
<tr>
<td>Small, simplified equipment, easily adapted to facilitate (new) PAT equipment</td>
<td>Large Scale, complex equipment, often multi purpose</td>
</tr>
<tr>
<td>Can we detect a bad batch?</td>
<td>Is this a good batch?</td>
</tr>
<tr>
<td>Scientists, chemometricians trained to operate analytical equipment</td>
<td>Skilled operators trained to operate manufacturing equipment</td>
</tr>
<tr>
<td>Transferred to manufacturing after 2-4 years</td>
<td>Manufactured for 5+ years</td>
</tr>
</tbody>
</table>
**Quality by Design Approach**

Project was a pilot for Quality by Design within Organon/SP legacy

A Quality by Design approach was applied in the development of the manufacturing process of the drug product to:

- Deliver a robust manufacturing process on commercial scale
- Provide flexibility in the supply chain (e.g. site, scale)
- Facilitate post-approval changes

**Quality by Design elements in the Application:**

- Quality risk management
- Quality target product profile
- Comprehensive control strategy DP
- Design space for manufacturing process DP
- On-line NIR application for blend uniformity control

**Specific Health Authorities guidance meetings on QbD:**

- March 2007 FDA Type C Guidance Meeting
- June 2007 EMEA PAT team Scientific Advice Meeting
- March 2009 FDA Type C Guidance Meeting
## Boundary conditions

<table>
<thead>
<tr>
<th>PRODUCTION SITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dev</td>
</tr>
<tr>
<td>Operations 1</td>
</tr>
<tr>
<td>Operations 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mixing Class/subclass</th>
<th>Dev</th>
<th>Operations 1</th>
<th>Operations 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion mixer, drum blenders/bin blenders</td>
<td>Convection mixer, orbiting screw blender</td>
<td>Diffusion mixer, bin blenders</td>
<td></td>
</tr>
<tr>
<td>Convection mixer, orbiting screw blender</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unit dosing Class/subclass</th>
<th>Dev</th>
<th>Operations 1</th>
<th>Operations 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet press, power assisted feeding</td>
<td>Tablet press, centrifugal feeding</td>
<td>Tablet press, power assisted feeding</td>
<td></td>
</tr>
<tr>
<td>Tablet press, centrifugal feeding</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coating Class/subclass</th>
<th>Dev</th>
<th>Operations 1</th>
<th>Operations 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan coating, perforated coating system</td>
<td>Pan coating, perforated coating system</td>
<td>Equipment to be purchased (perforated coating system)</td>
<td></td>
</tr>
<tr>
<td>Pan coating, perforated coating system</td>
<td></td>
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</tr>
</tbody>
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MSD
Strategy

► Use Quality by Design and Design Space concept to create desired flexibility in:
  – Equipment (mixing, compression)
  – Batch size (mixing, coating)
  – Manufacturing site
  – Real time Release

While ensuring quality
A control strategy

INPUTS

- PSD Excipients
- PSD Active
- Moisture content excipients
- RH
- Batch size
- Mixer type

Parameters

- Mixing time
- Mixing speed
- Blend uniformity
- Critical
The desired control strategy

INPUTS

- PSD Excipients
- PSD Active
- Moisture content excipients
- RH
- Batch size
- Mixer type

Parameters

- Mixing time
- Mixing speed

NIR

MIXING

- Blend uniformity

INPUTS Parameters

- Critical for this unit operation
- Not critical
- Critical for other unit operation
## Process control, dry mixing

<table>
<thead>
<tr>
<th>Process Step</th>
<th>Process Control</th>
<th>Method</th>
<th>Acceptance Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing</td>
<td>Blend uniformity</td>
<td>NIR</td>
<td>• F-critical value corresponding to an α-error of 5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• The minimum mixing time is 15 min&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• The acceptance range for total mixing time is 20 -180 minutes&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> to prevent false positive results for the F-test.

<sup>2</sup> if the NIR control does not indicate a uniform blend after 180 minutes, the blending will be stopped manually and stratified sampling of uncoated tablets post-compression will be conducted to confirm content uniformity using the following criteria: RSD is less than 5% and mean content is 95.0 – 105.0% (n = 3, 20 locations).
Feedback EMA

Based on assessment reports and day 120 final List of Questions

No major issues observed, 49 concerns

Acceptance in dossier of:
- NIR application for control of blend uniformity
- Stratified sampling results in lieu of Uniformity of dosage unit tests
- Clinically relevant dissolution specification of Active
- Risk scoring and acceptance of all risks prior to commercial production
- Design space containing two mixer types (diffusion and convection) and batch size range
- Comprehensive control strategy
In case of NIR failure, strategy will be to refer to pre-established blending times. Thus, *it should be demonstrated* that the set blending times adequately cover the potential interactions between relevant variable attributes (in particular nomegestrol acetate and excipients particle size) and/or parameters (in particular blend speed and shear force).
## Summary

<table>
<thead>
<tr>
<th></th>
<th>EMA</th>
<th>FDA</th>
<th>TGA</th>
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</thead>
<tbody>
<tr>
<td>Design Space</td>
<td>😞</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>NIR control</td>
<td>😊</td>
<td>😞</td>
<td>😊</td>
</tr>
<tr>
<td>Batch size range, mixing</td>
<td>😊</td>
<td>😊</td>
<td>😊</td>
</tr>
<tr>
<td>Bin blender</td>
<td>😞</td>
<td>😞</td>
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</tbody>
</table>
An efficient, maintenance free and approved method for spectroscopic control and monitoring of blend uniformity: The moving F-test

Rut Besseling\textsuperscript{a,b,c}, Michiel Damen\textsuperscript{a,b}, Thanh Tran\textsuperscript{c}, Thanh Nguyen\textsuperscript{a,d}, Kaspar van den Dries\textsuperscript{a,c}, Wim Oostra\textsuperscript{a,f}, Ad Gerich\textsuperscript{a,b}

Time check….

- **Go to conclusion and Q&A**
- Discuss legacy products
LEGACY PRODUCTS
Lifecycle approach for legacy products

Perform comprehensive review of Process Control Strategy (PCS), historical production data trends, and events-based data/information (deviations, complaints, etc).

Is the legacy manufacturing process well controlled? *

YES

Continue to monitor/trend on a routine basis. Ensure events-based data are integrated.

NO

Use process knowledge, risk assessment, and/or historical data to identify sources of process variability and/or PCS deficiencies.

Can process variability be reduced via minor process change and/or addition of process controls?

YES

Implement change and continue collecting CPV data to confirm that variability is reduced.

NO

Can process variability be reduced via significant process changes which are supported by existing data?

YES

Implement changes Re-perform PPQ.

NO

Perform Process Design work required to support process changes necessary for ensuring process control.

* Is an appropriate Process Control Strategy (demonstrating understanding of the impact of process parameters on CQAs) defined and does statistical of data show that variability is controlled?
Legacy product

• Product description
  • combines a *slow release* formulation of a calcium channel blocker, and an immediate release formulation of an angiotensin converting enzyme inhibitor

• Double layer tablet

• Approved 1996
Problem definition

• Issues in a manufacturing site with dissolution stability, at release and during shelf life
• Manufacturing process cumbersome (granulator difficult to empty/clean, wet screening now and then “spaghetti”)
• Problem not seen in all locations
Problem Definition

4-hour dissolution of production samples over 2010-2012 as a function of batch order. The green, black and Red lines correspond to min, mean and max of 6 samples (or 12 in case a transgression of the upper specification limit was observed in the first 6)

*Upper and lower specification*
Elements of QbD

- QTPP
- Risk assessments (should be *management*)
- CQA’s
- CPP’s
- Control strategy
- Design space
- Continuous improvement
EXCIPIENTS

Granulation ingredients

API

MCC

Povidone

Sodium alginate

PROCESS

Granulation process

Dissolution method

Density

Temperature

pH

Hydrodynamics

Paddle speed

4-hr dissolution of coated tablets

Focus of pilot batches

Points for investigation

API → Povidone

MCC → Viscosity, K-type

Povidone → Viscosity, K-type

Granulation process → Variability

Sizing → Drying

Sizing → Blending

Lubrication → Coating

Points for investigation

Focus of pilot batches

Average

Average

Average

Average

Average

Average

Average

Average

Average

Average

Average

Average

Average

Average

Average

Average
Commercial scale, dissolution

- Mean well centered, min-max close to spec
Commercial scale, dissolution

Mean = 46.7%
s.d. = 4.8%

Mean = 45.2%
s.d. = 3.5%

Cores s.d.: 0.8-1.5%
Cores vs. coated

• Significant differences were seen between standard deviation in cores and coated tablets (1% vs. 4-5%)
• Collected coating conditions of all sites
• Investigated effect of process and coat materials
  – Heating
  – Spraying, water, coat solution
  – Type of coat PVA based, HPMC based
  – Wax addition cold vs. Warm tablets
Cores vs coated

4 hr dissolution
Investigation of coat-disso relation

- Used OCT, NIR, THz
- Initial data suggested correlation between coat quality and dissolution, extended data set with more batches confirmed variability in coat thickness, (talc) and surface roughness but was inconclusive wrt correlation with dissolution
Results
Dissolution – Data, new method
Elements of QbD

- QTPP
- Risk assessments (should be *management*)
- CQA’s
- CPP’s
- Control strategy
- Design space
- Continuous improvement
Legacy products

• Generally not designed per QbD (but many still very well designed!), may lack QbD terminology
• Generally many years of manufacturing experience and data available, allowing a good assessment of variability!
• Various “maintenance” activities can trigger product upgrade:
  • Introduction of new suppliers of ingredients
  • Site transfers
  • Product issues
How far are we?

MAKING DO IN MAKING DRUGS: INNOVATION POLICY AND PHARMACEUTICAL MANUFACTURING

W. NICHOLSON PRICE II

Abstract: Despite increasing recalls, contamination events, and shortages, drug companies continue to rely on outdated manufacturing plants and processes. Drug manufacturing’s inefficiency and lack of innovation stand in stark contrast to drug think we have reached that goal. Over the past decade, the regulations and the regulators have not really adapted that much.”382 FDA Commissioner Margaret Hamburg reiterated this view in February 2013, stating, “[I]n a world where quality risk management is fully embraced, we could foresee a time when enhanced regulatory flexibility might be possible.”383 Thus, meaningfully
Mini review
FDA pharmaceutical quality oversight
Lawrence X. Yu*, Janet Woodcock
Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20903, USA

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ABSTRACT
The launch of the Center for Drug Evaluation and Research (CDER) Office of Pharmaceutical Quality (OPQ) is a milestone in FDA’s efforts to assure that quality medicines are available to the American public. As a new super-office within CDER, OPQ is strategically organized to streamline regulatory processes, advance

1. Product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design; these data further indicate failures in the implementation of manufacturing process scale-up as well as routine production.

2. There have been alarming shortages of critical drugs over the past few years. Many of these shortages were caused by the use of outdated equipment, reliance on aging facilities operating at maximum production capacity, and lack of effective quality management systems.

3. The number of post-approval supplements received for review has increased over the past decade, in part owing to our current practice of “locking in” an applicant’s manufacturing process before it is fully optimized. A burdensome regulatory
2017

• Quality by Design, Revolution or Evolution?
  – Discussion, questions....