Quality-by-design of nanopharmaceuticals. A state of the art
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Quality-by-Design of Nanopharmaceuticals. A State of the Art

T. Bastogne | CRAN CNRS-Univ. Lorraine | INRIA BIGS | CYBERNANO
JRC, Ispra, Italy, 27-28 Sep
Contents

1. QbD in Theory
3. One perspective...
7 compounds
2 parameters
3 tested values

$3^{(7 \times 2)} > 4 \times 10^6$
formulations

6 production units
3 parameters
3 tested values

$3^{(6 \times 3)} > 3 \times 10^9$
nano-products
Risk Management

A large population of possible different Nano-objects

**EFFICACY:**
Ho: Nano is not Efficient  
H1: Nano is Efficient

**SAFETY:**
Ho: Nano is not Toxic  
H1: Nano is Toxic

Prob[Efficacy|Data]?

Prob[Safety|Data]?

How to minimize the risks of bad decisions?

Quality-by-Design: an approach to estimate and control those risks  
ICH Q8,Q9,Q10
Historical background

- Aeronautics & Automotive Industries: Total Quality Management, Design for Six-Sigma
- FDA officials realized that biologics and drugs could also stand to benefit from QbD.
- **Concept paper** on 21st Century Good Manufacturing Practices.
- FDA produced a **guidance** document: «Pharmaceutical cGMPs for the 21st Century»
- ICH published the **Guideline document**: Q8 (R2): Pharmaceutical Development.
- Now adaptation for Biomedical Devices & Analytical Methods*

*S. Chatterjee, QbD Considerations for Analytical Methods - FDA Perspective, IFPAC Annual Meeting, Baltimore, Jan 2013
A risk-based project management:

- 6 main tasks
- 6 main deliverables
- 4 go / no go tests
A risk-based project management:

- 6 main tasks
- 6 main deliverables
- 4 go/no go testing
QbD-1: Profile your Nano

- Name
- Dosage Form
- Route Of Administration
- Dosage Strength
- Pharmacokinetics
- Clinical Intended Use
- Reference Listed Drug
- Scale Of Production
- Safety Concerns

QTPP
Quality Target Product Profile
QbD-2: Quality Attributes?

To measure potential consequences we need to define relevant QA. QA = physico-chemical or biological property to be controlled to ensure to get the expected quality/safety/efficacy requirement.

Critical Quality Attributes?

How? Prior Risk Analysis (Failure Mode & Effect Analysis)
Which are the most influential factors that could cause variability of CQA?

CMA
Critical Material Attributes

CPP
Critical Process Parameters

How? Design of Experiments for Factor Screening
QbD-4: Design Space?

CQA = f(CMA, CPP)

How? Design of Experiments for Response Surface Modeling
QbD-5: Control Strategy?

How? Statistical Process Control
QbD-6: Product LifeCycle Management

How? PLM Methods (Product LifeCycle Management)
In Practice?
In practice?

- Bibliographic engine: Web of Science
- Keywords: nano, quality-by-design & drug delivery
- Replication: every 6 months
- 30 identified articles between 2007 and 2017


This work was supported by the European Union and the ERA-NET framework under the EuroNanoMed II project NanoBiT.
Where in practice?

1. Asia (44%)
2. USA (28%)
3. Europ (15%)
4. Africa & Middle East (13%)
1) QTPP

- Frequency: 5/30 (16.7%)
- Since 2015

<table>
<thead>
<tr>
<th>QTPP of a gel with polymeric nanoemulsified particles</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Hydrogel</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Injection</td>
</tr>
<tr>
<td>Dosage strength</td>
<td>% of drug substance (% w/w)</td>
</tr>
<tr>
<td>Dosage form design</td>
<td>Polymeric nanoemulsified carriers incorporated into hydrogel</td>
</tr>
<tr>
<td>Pharmacokinetics Stability</td>
<td>Bioequivalent to reference-listed drug</td>
</tr>
<tr>
<td>Stability</td>
<td>Shelf life not &lt;24 months at room temperature</td>
</tr>
<tr>
<td>Drug product quality attributes</td>
<td>Physical attributes, identification, assay, uniformity of content, degradation products, residual solvents, dissolution, microbiological quality, pH, and rheological behavior</td>
</tr>
<tr>
<td>Container closure system</td>
<td>Suitable container closure system that will support estimated shelf life and drug product integrity during the transport, Identical primary packaging as reference-listed drug product</td>
</tr>
<tr>
<td>Alternative methods of administration</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Profile component

<table>
<thead>
<tr>
<th>Profile component</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Nanoparticles</td>
<td>Novel dosage form for targeted drug delivery</td>
</tr>
<tr>
<td>Dosage design</td>
<td>Sustained release nanoparticles</td>
<td>For long-term treatment of RZT</td>
</tr>
<tr>
<td>Particle size (nm)</td>
<td>350-650</td>
<td>Narrow distribution</td>
</tr>
<tr>
<td>Entrapment efficiency (%)</td>
<td>&gt;50</td>
<td>Higher entrapment is better for the nanoparticulate dosage form</td>
</tr>
<tr>
<td>Drug release (h)</td>
<td>&gt;48</td>
<td>To achieve sustained drug release for long period of time</td>
</tr>
</tbody>
</table>

RZT: Rizatriptan, QTPP: Quality target product profile, CS: Chitosan

A.E. Shirsat & S.S. Chitlange, 2015

A.S. Zidan, 2016
2) CQA Specification

5 main Critical Quality Attributes (70%)

1. NP Size
2. Encapsulation Efficiency
3. Polydispersity Index
4. Zeta Potential
5. Amount of Release
### 3) CMA Specification

6 Critical Material Attributes > 90%

1. Ingredient Concentration
2. Ingredients Ratio
3. Drug Load
4. Surfactant Concentration
5. Ingredient Type
6. Surfactant Type

![Graph showing frequency and cumulative percentage for various attributes](image_url)

**Graph Details:**

- **Y-axis:** Frequency
- **X-axis:** Various attributes:
  - Ingredient Conc.
  - 2-Ingredients Ratio
  - Drug Load
  - Surfactant Conc.
  - Ingredient Type
  - Surfactant Type
  - pH of Aq. Phase
  - Size Load. Particles

**Cumulative Percentage:**

- 0%
- 25%
- 50%
- 75%
- 100%

**X-axis:**

- 0
- 10
- 20
- 30

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T Bastogne, JRC-Ispra 27-28 Sep 2017
4) CPP Specification

- No really dominant CPP
- Process dependant
5) Prior Risk Analysis

- Frequency: 5/30 (16.7%)
- Since 2015

![Ishikawa diagram illustrating CPP affecting on CQA of RHT SLN.](image)

Table 1
Initial risk assessment for ACE-NLCs.

<table>
<thead>
<tr>
<th>Drug product CQAs</th>
<th>Conc. of Solid lipid</th>
<th>Conc. of Tween 80</th>
<th>Conc. of liquid lipid</th>
<th>Ratio of PL: Ethanol</th>
<th>Water</th>
<th>Stirring time</th>
<th>Stirring speed</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle Size</td>
<td>High</td>
<td>High</td>
<td>Med</td>
<td>High</td>
<td>Med</td>
<td>Med</td>
<td>Med</td>
<td>Low</td>
</tr>
<tr>
<td>Permeation Flux</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Release</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Entrapment</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Med</td>
<td>Med</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Criticity = Severity x Frequency

N.K. Garg et al., 2017

B. Shah et al., 2015
Measurement Technologies

4 main measurement techno. > 50%

1. Dyn. Light Scattering
2. HPLC
3. Trans. Electro. Microscopy
4. X-Ray Diffraction
Design of Experiments

- Many inconsistencies between DoE methods and objectives
- A good software is necessary but not enough! Expertise is needed
- Confidence of the results requires to apply strictly validation procedures.
- Only 5/30 papers have really implemented a cross-validation step
And after?

• The Design Space is not the ultimate goal. The last part of the QbD lifecycle is totally forgotten.

• No control strategy
• No continuous quality management

• Difficulty to implement on-line measurement technologies
• Another community: production & control engineering
The Quality-by-Design approach is more and more adopted in the *nano-community* mainly in India and USA. Nevertheless, some important parts, e.g. control strategy & quality management, are still ignored. Statistical tools exist but they are not always used correctly → educational effort is needed. QbD success relies on the synergistic relationships between chemists, physicists, biologists, statisticians and engineers.
Towards a new Cardio/Neuro-Toxicity Testing Model for Nano-Products

- **CiPA**: FDA, HESI, CSRC, SPS, EMA, Health Canada, Japan NIHS, PMDA
- Objective: revise the current guidelines for evaluating a pharmaceutical drugs tendency to induce cardiac arrhythmias (ICH S7B).

1. **CiPA**: Comprehensive in vitro Proarrythmia Assay
Special thanks to my collaborators ...

- M. Beckler, L. Doerr, N. Fertig (Nanion, D) [1,4]
- A. Fouassier (Ncardia, NL-D) [3]
- L. Guo (Frederick Nat Lab, NIH/NCI, US) [5]
- F. Atienzar, A. Deleaunois, J.-P. Valentin (UCB, B) [3]
- P. Voiriot, A. Durand-Salmon (Cardiabase, F) [2]
- L. Batista, P. Guyot (Cybernano, F) [1,2,3,4,5]
- M. Barberi-Heyob (CRAN, CNRS, F)
- A. Gégout-Petit (INRIA BIGS, F)

To sum up …

• QbD = Hollistic approach of drug development
• From predefines objectives to full-scale production
• Risk-based approach

A good Tool for QbD is not enough !

• Guidance ≠ Methodology
• Needs an efficient Collaboration between users
• Requires a Statistical Background
  • Prior Risk Analysis
  • Design of Experiments
  • Multivariate Analysis
  • Control Theory

Practibility for Nanomedicine ?