Quality-by-design of nanopharmaceuticals. A state of the art
Thierry Bastogne

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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...
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
QbD LifeCycle

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.

Low Risk

QA

QA / CQA?

High Risk

CQA

Critical Quality Attributes?

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

**How?** Design of Experiments for Factor Screening

**CMA**
Critical Material Attributes

**CPP**
Critical Process Parameters

**QbD-3: Formulation & Production Factors?**
QbD-4: Design Space?

CQA = f(CMA, CPP)

Design Space

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

Control? ➔ Process

Profile your Drug

Identify Quality Attributes ➔ Criticity Analysis

Identify Risk Factors ➔ Criticity Analysis

Determine Region of Quality/Safety

Model Quality? ➔ CMA Critical Material Attributes ➔ CPP Critical Process Parameters

Establish Control Strategy

Manage Product Lifecycle

Design Space

Process Analytical Technology

Project End

Requirement Assessment

DS Critical Quality Attributes

CMA Critical Material Attributes

CPP Critical Process Parameters

DS Design Space

Product Formulation & Process Management

Identify Risk Factors

CQA Critical Quality Attributes

QTPP Qualitative Target Product Profile

Profile your Drug

Project Start

How? Statistical Process Control

T Bastogne, JRC-Ispra 27-28 Sep 2017
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

### QTPP of a gel with polymeric nanoemulsified particles

<table>
<thead>
<tr>
<th>QTPP elements</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Hydrogel</td>
<td>Pharmaceutical equivalence requirement: same dosage form</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Injection</td>
<td>Pharmaceutical equivalence requirement: same route of administration</td>
</tr>
<tr>
<td>Dosage strength</td>
<td>% of drug substance (% w/w)</td>
<td>Pharmaceutical equivalence requirement: same dosage strength</td>
</tr>
<tr>
<td>Dosage form design</td>
<td>Polymeric nanoemulsified carriers incorporated into hydrogel</td>
<td>Match reference-listed drug product</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Bioequivalent to reference-listed drug</td>
<td>Match reference-listed drug product</td>
</tr>
<tr>
<td>Stability</td>
<td>Shelf life not &lt; 24 months at room temperature</td>
<td>Equivalent or longer shelf life compared to reference-listed drug product</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>
<td>Pharmaceutical equivalence requirement: fulfill the same quality standards as reference-listed drug product</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>
<td>Vials or prefilled syringes, similar with reference-listed drug product, acceptable for the patient</td>
</tr>
<tr>
<td>Alternative methods of administration</td>
<td>No</td>
<td>None are listed on reference drug product labeling</td>
</tr>
</tbody>
</table>

**Profile component**  | **Target**                    | **Justification**                                                                 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></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
4) CPP Specification

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

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

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>

Risk estimation matrix

- High risk parameter
- Medium risk parameter
- Low risk parameter

Fig. 1. Ishikawa diagram illustrating CPP affecting on CQA of RHT SLN.

Criticity = Severity x Frequency

B. Shah et al., 2015

N.K. Garg et al., 2017
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
Conclusion

• 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?