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

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Bridging communities in the field of nanomedicine

European Commission, Joint Research Centre (JRC)
27-28 Sep. 2017, Ispra, Italy

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
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Core Material
Core Size
Targeting Molecule Type
Targeting Molecule Concentration
Coating Ingredient
Coating Ingredient Concentration

Unit 1
Emulsification

Unit 2
Polymerisation

Unit 3
Coating

Unit 4
Evaporation

Unit 5
Heat

Unit 6
Packaging

Sonication Time
Sonication Amplitude
Sonication Power
Polymerization Time
Polymerization Temperature
Polymerization RPM
Coating Concentration
Coating Time
Coating Temperature
Evaporation Time
Evaporation Temperature
Evaporation RPM
Heat Time
Heat Temperature
Packaging Support
Packaging Volume

7 compounds
2 parameters
3 tested values

$3^{(7 \times 2)} > 4.10^6$ formulations

6 production units
3 parameters
3 tested values

$3^{(6 \times 3)} > 3.10^9$ nano-products
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 & Automative 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)
QbD-3: Formulation & Production Factors?

Which are the most influent 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)

CMA

Design Space

CPP

How? Design of Experiments for Response Surface Modeling

T Bastogne, JRC-Ispra 27-28 Sep 2017
QbD-5: Control Strategy?

How? Statistical Process Control

Control?

Process
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

T. Bastogne, “Quality-by-design of nano-pharmaceuticals - A state of the art,”
Where in practice?

1. Asia (44%)
2. USA (28%)
3. Europe (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 (% of drug substance (% w/w))</td>
<td></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>

### Table 2: QTPP and CQA of target drug product, gel with polymeric nanoemulsified particles, for injection

<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
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.

B. Shah et al., 2015

Criticity = Severity x Frequency

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

- **CiPA¹**: 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 predefinites 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?