

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

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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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T Bastogne, JRC-Ispra 27-28 Sep 2017



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Prob[Safety|Data]?

Ho: Nano is not Toxic

H1: Nano is Toxic

SAFETY:

A large population of possible different Nano-objects

EFFICACY:

Risk Management

Ho: Nano is not Efficient H1: Nano is Efficient

Prob[Efficacy|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

QbD LifeCycle

A risk-based project management :

- 6 main tasks
- 6 main deliverables
- 4 go / no go tests



QbD LifeCycle

A risk-based project management :

- 6 main tasks
- 6 main deliverables
- 4 go / no go testing

















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 nanopharmaceuticals - A state of the art," Nanomedicine: Nanotechnology, Biology, and Medicine. June 2017.



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QdD Articles in Nanomedicine



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

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

QTPP of a gel with polymeric nanoemulsified particles						
QTPP elements	Target	Justification				
Dosage form	Hydrogel	Pharmaceutical equivalence requirement: same				
		dosage form				
Route of administration	Injection	Pharmaceutical equivalence requirement: same				
		route of administration				
Dosage strength	% of drug substance (% w/w)	Pharmaceutical equivalence requirement: same				
		dosage strength				
Dosage form design	Polymeric nanoemulsified carriers incorporated into hydrogel	Match reference-listed drug product				
Pharmacokinetics	Bioequivalent to reference-listed drug	Match reference-listed drug product				
Stability	Shelf life not ${<}24$ months at room temperature	Equivalent or longer shelf life compared to				
		reference-listed drug product				
Drug product quality attributes	Physical attributes, identification, assay,	Pharmaceutical equivalence requirement: fulfill the				
	uniformity of content, degradation products,	same quality standards as reference-listed drug				
	residual solvents, dissolution, microbiological	product				
	quality, pH, and rheological behavior					
Container closure system	Suitable container closure system that will	Vials or prefilled syringes, similar with reference-				
	support estimated shelf life and drug product	listed drug product, acceptable for the patient				
	integrity during the transport, Identical primary					
	packaging as reference-listed drug product					
Alternative methods of administration	No	None are listed on reference drug product labeling				

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

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

A.S. Zidan, 2016



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 Criticial 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



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

Table 1Initial risk assessment for ACE-NLCs.

	Risk estimation matrix								
Drug product CQAs	Conc. of Solid lipid	Conc. of Tween 80	Conc. of liquid lipid	Ratio of PL: Ethanol	Water	Stirring time	Stirring speed	Temp	
Particle Size	High	High	Med	High	Med	Med	Med	Low	
Permeation Flux	High	High	High	High	Med	Low	Low	Low	
Release	High	High	High	High	Med	Low	Low	Low	
Entrapment	High	High	High	Med	Med	Low	Low	Low	

High risk parameter,

Medium risk parameter, **E** Low risk parameter.

Measurement Technologies

4 mian measurement techno. > 50%

- 1. Dyn. Light Scaterring
- 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



Design space for rizatriptan loaded chitosan nanoparticles



And after ?

- The Design Space is not the ultimate goal. The last part of the QbD lifecyle 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.
- ObD 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**¹: FDA, HESI, CSRC, SPS, EMA, Health Canada, Japan NIHS, PMDA
- Objective: revise the current guidelines for evaluating a pharmaceutical drugs tendency to induce cardiac arrythmias (ICH S7B).



- 1. CiPA: Comprehensive in vitro Proarrythmia Assay
- J. D. Strickland, W. R. Lefew, J. Crooks, D. Hall, J. N. Ortenzio, K. Dreher, and T. J. Shafer, "In vitro screening of metal oxide nanoparticles for effects on neural function using cortical networks on microelectrode arrays," Nanotoxicology, vol. 10, no. 5, pp. 619– 628, 2016.

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- 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)



[1] L. Bastista, L. Doerr, M. Beckler, N. Fertig, and T. Bastogne, "Coupled impedance & field potential data analysis of in vitro cardiomyocyte assays," in Proc of the SPS Annual Meeting, (Berlin, Germany), September 24-27 2017.

[2] P. Guyot, P. Voiriot, S. Papelier, L. Batista, and T. Bastogne, "A comparison of methods for delineation of wave boundaries in 12 lead ecg," in Proc of the SPS Annual Meeting, (Berlin, Germany), September 24-27 2017.

[3] L. Bastista, T. Bastogne, F. Atienzar, A. Delaunois, and J.-P. Valentin, "A data-driven modeling method to analyze cardiomyocyte impedance data," in Proc of the SPS Annual Meeting, (Berlin, Germany), September 24-27 2017.

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[5] L. Guo, M. Furniss, J. Hamre, L. Batista, T. Bastogne, Z. Yan, J. Wu, S. Eldridge, and M. Davis, "Assessing functional and structural cardiotoxicity in cultured human ipsccardiomyocytes," in Proc of the SPS Annual Meeting, (Berlin, Germany), September 24-27 2017.

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 ?

