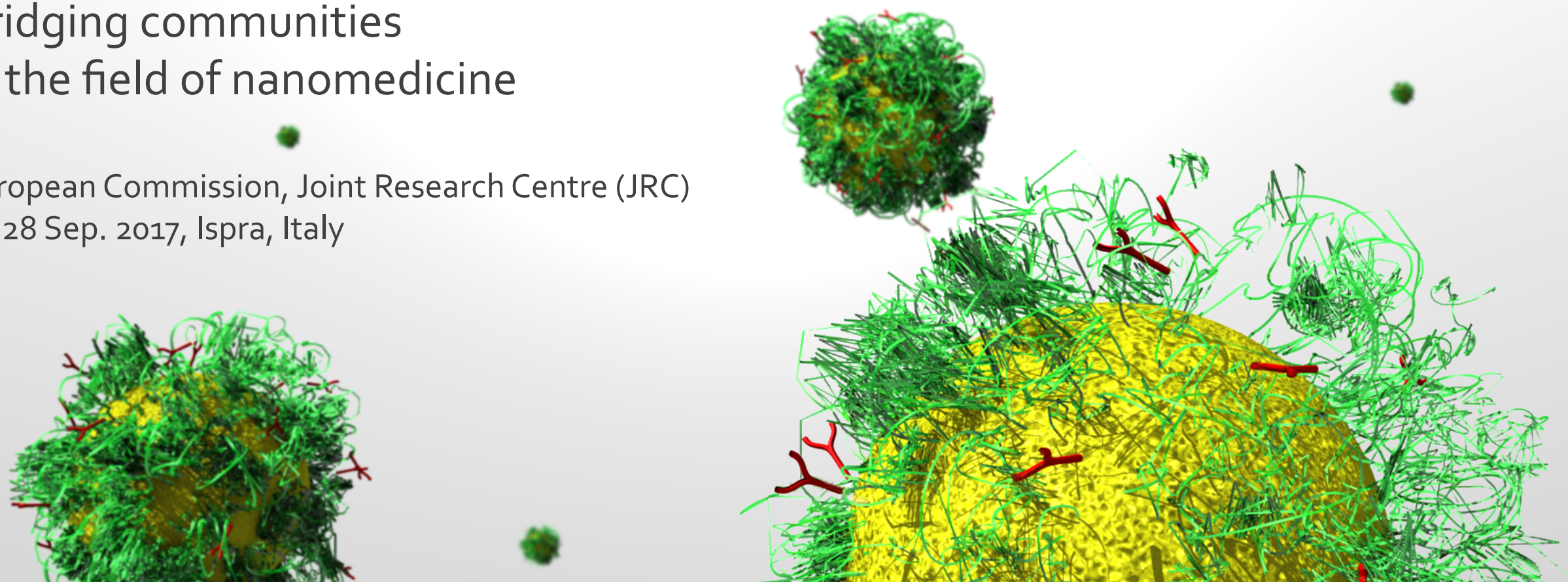
Quality-by-design of nanopharmaceuticals. A state of the art

Thierry Bastogne

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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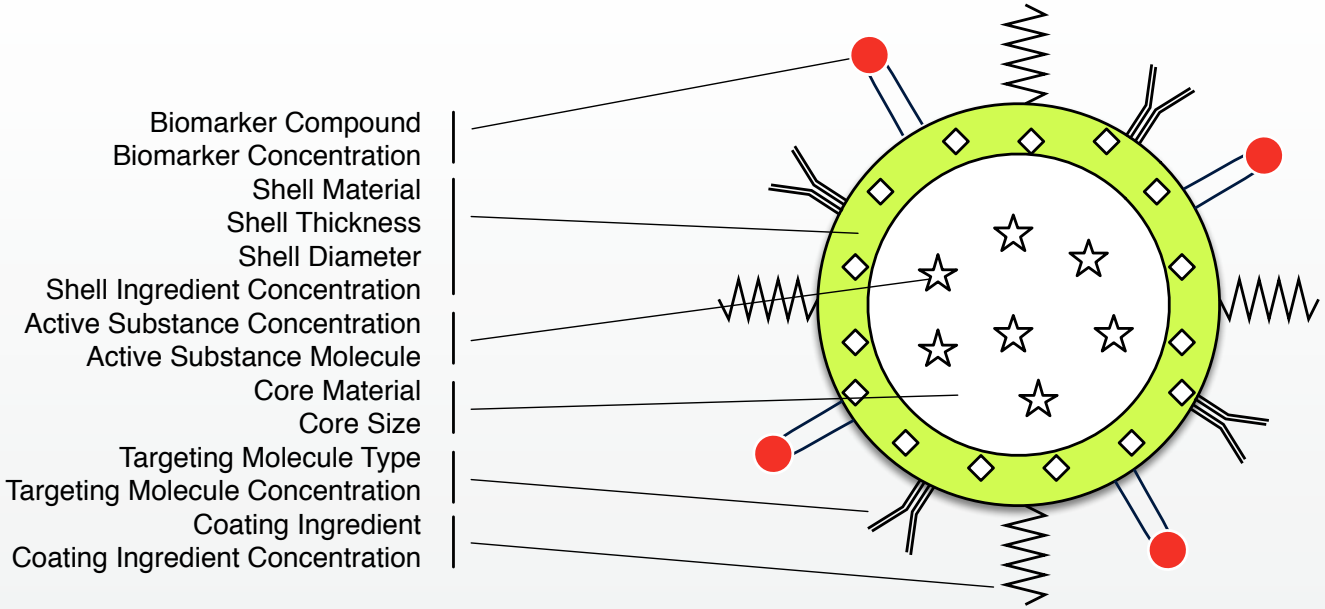
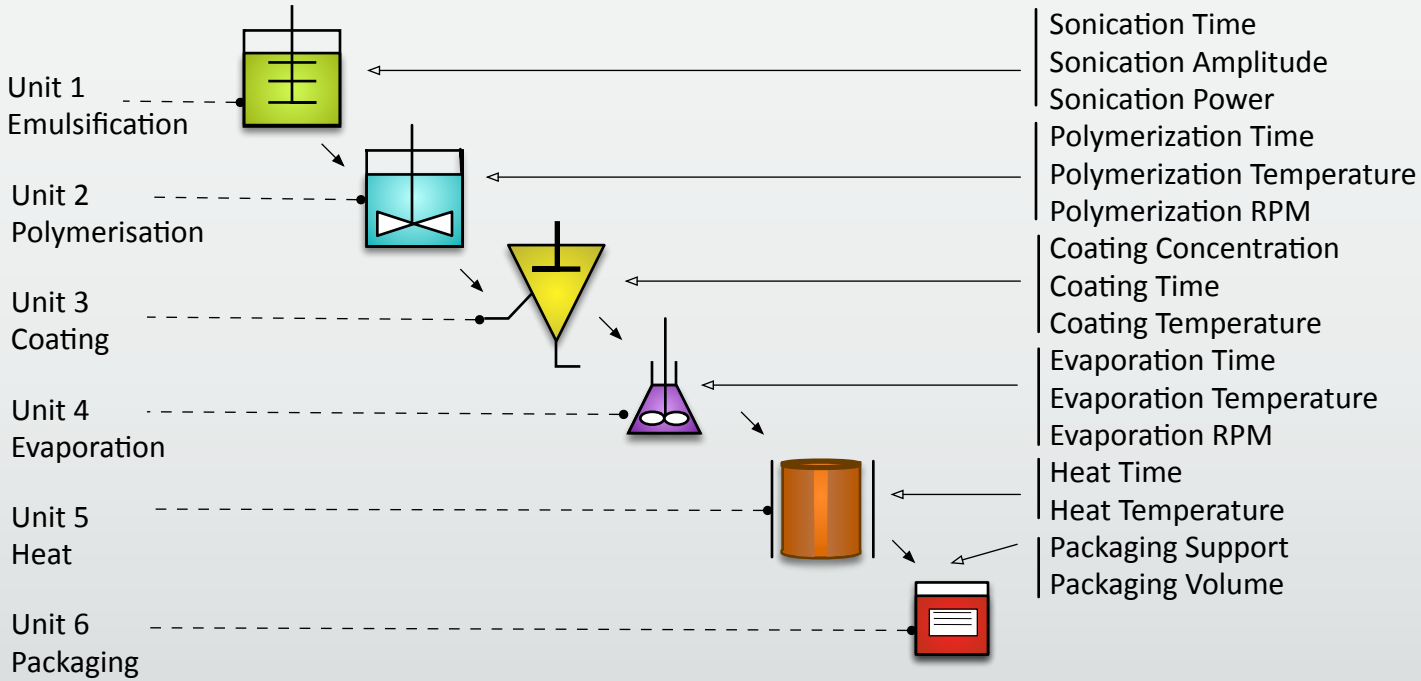


7 compounds
2 parameters
3 tested values

$3^{(7x2)} > 4.10^6$ formulations

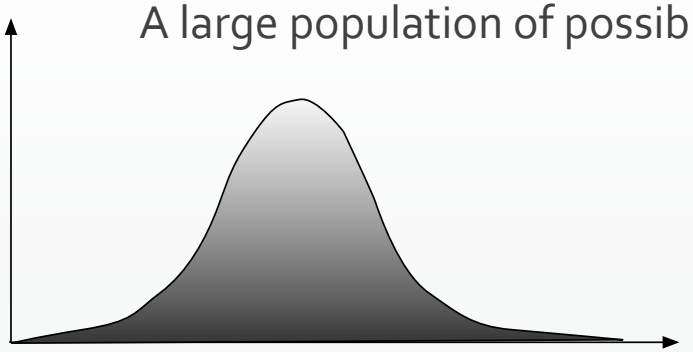


6 production units
3 parameters
3 tested values

$3^{(6x3)} > 3.10^9$ 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

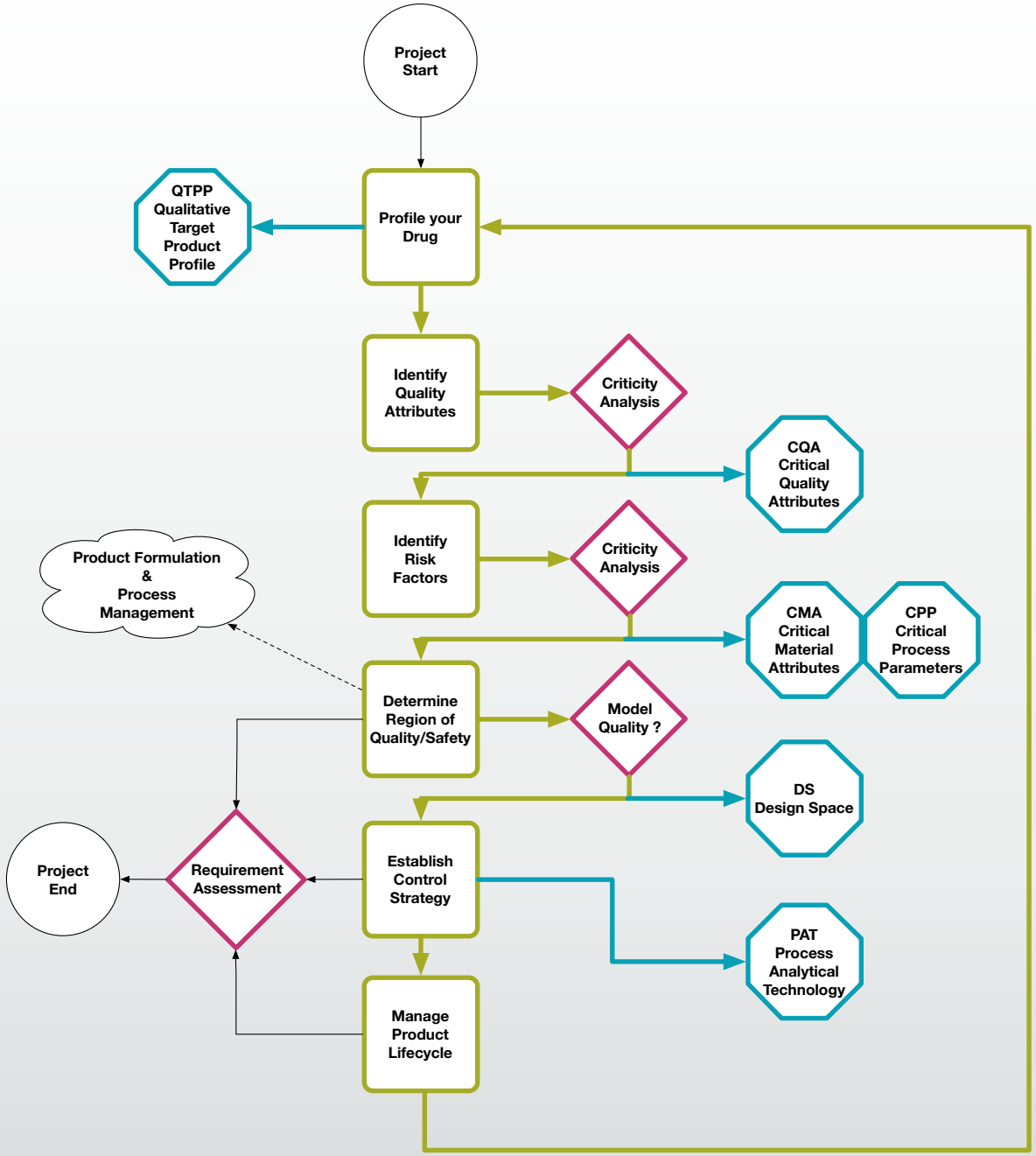
- Aeronautics & Automative Industries : Total Quality Management, Design for Six-Sigma
- FDA officials realized that biologics and drugs could also stand to benefit from QbD.
- **Concept paper** on 21st Century Good Manufacturing Practices.
- FDA produced a **guidance** document : « Pharmaceutical cGMPs 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

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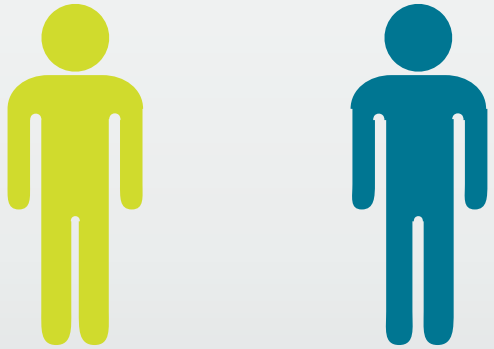
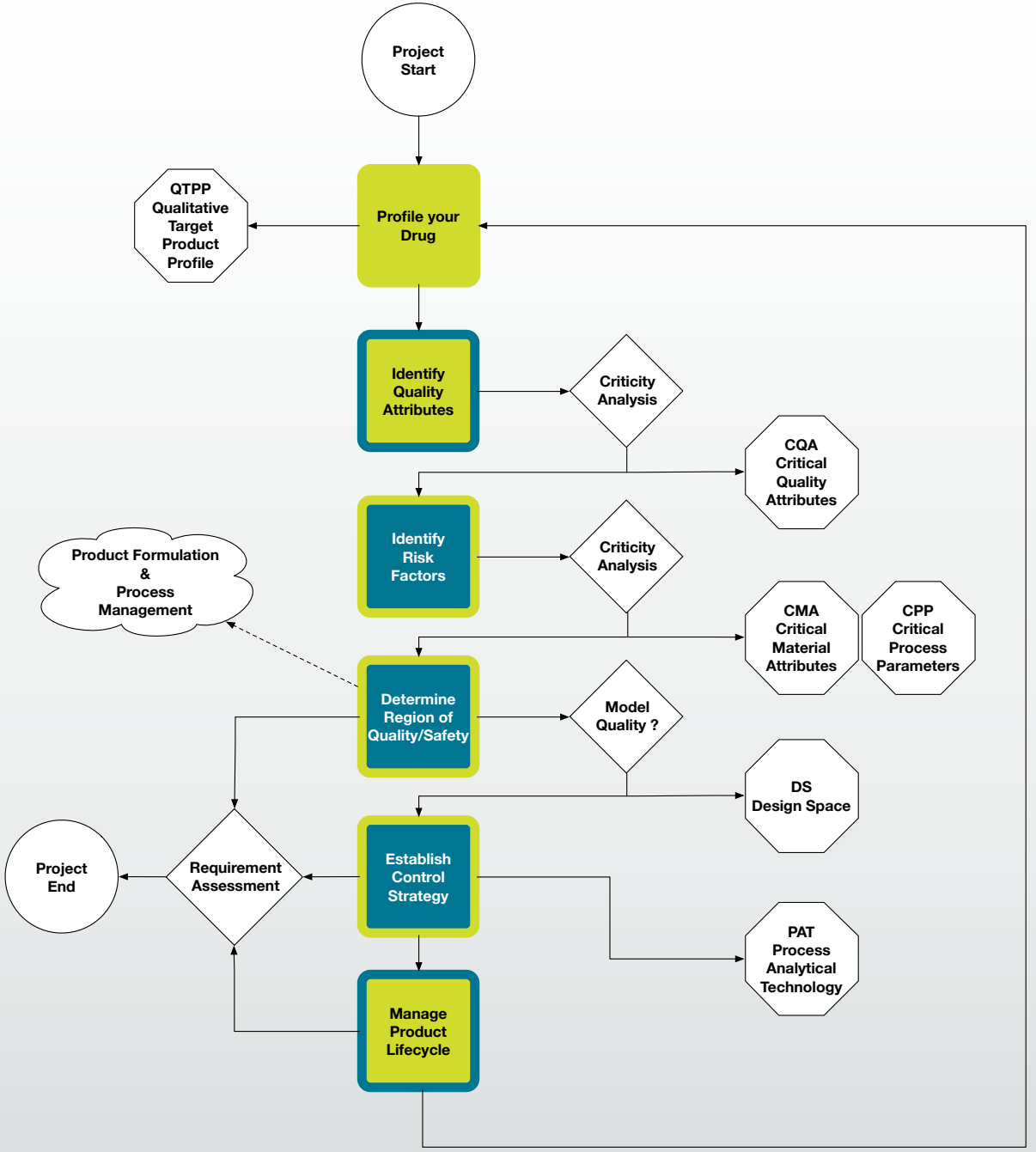


Life Scientist

Data Scientist

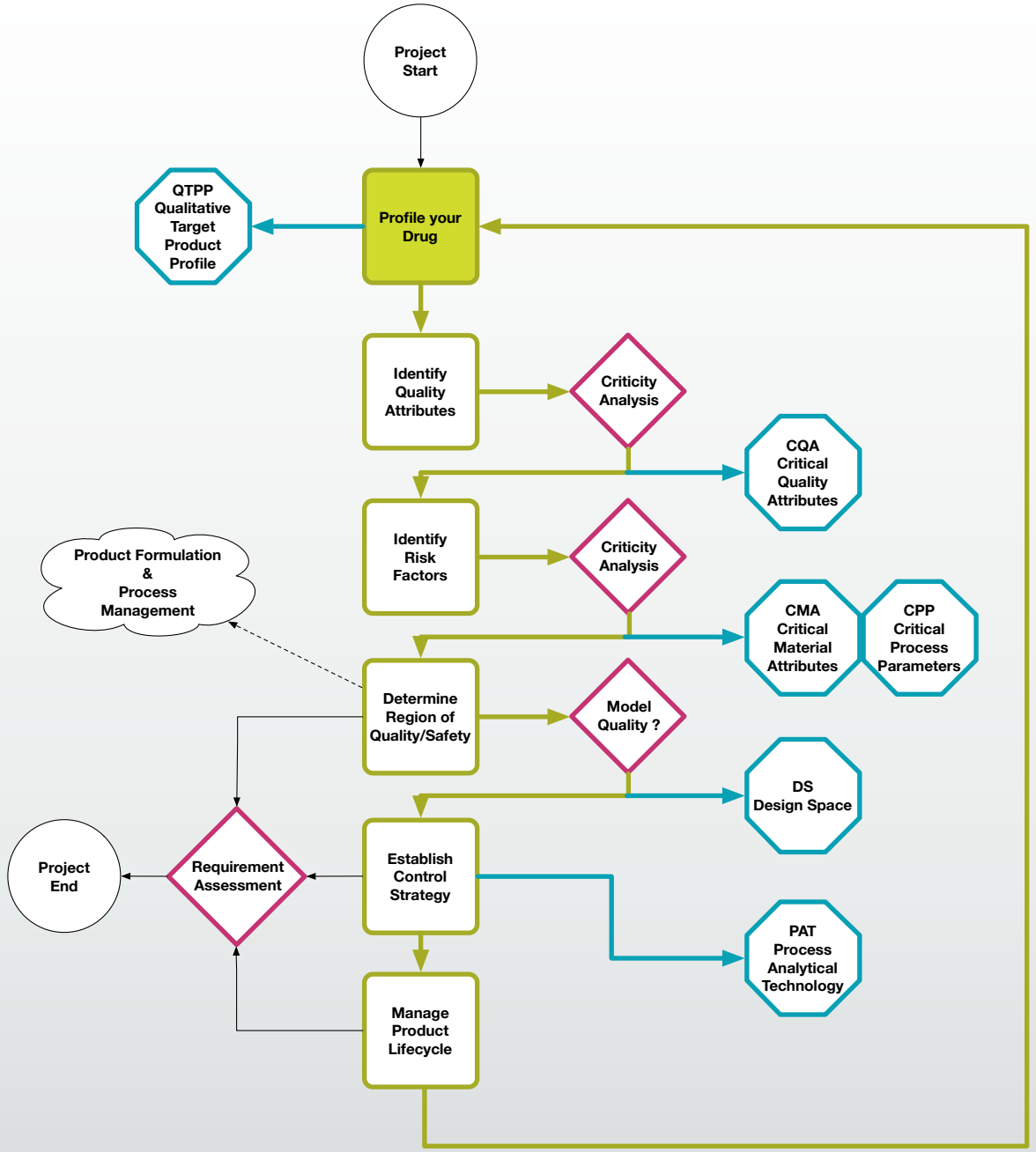


QbD-1: Profile your Nano

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

QTPP

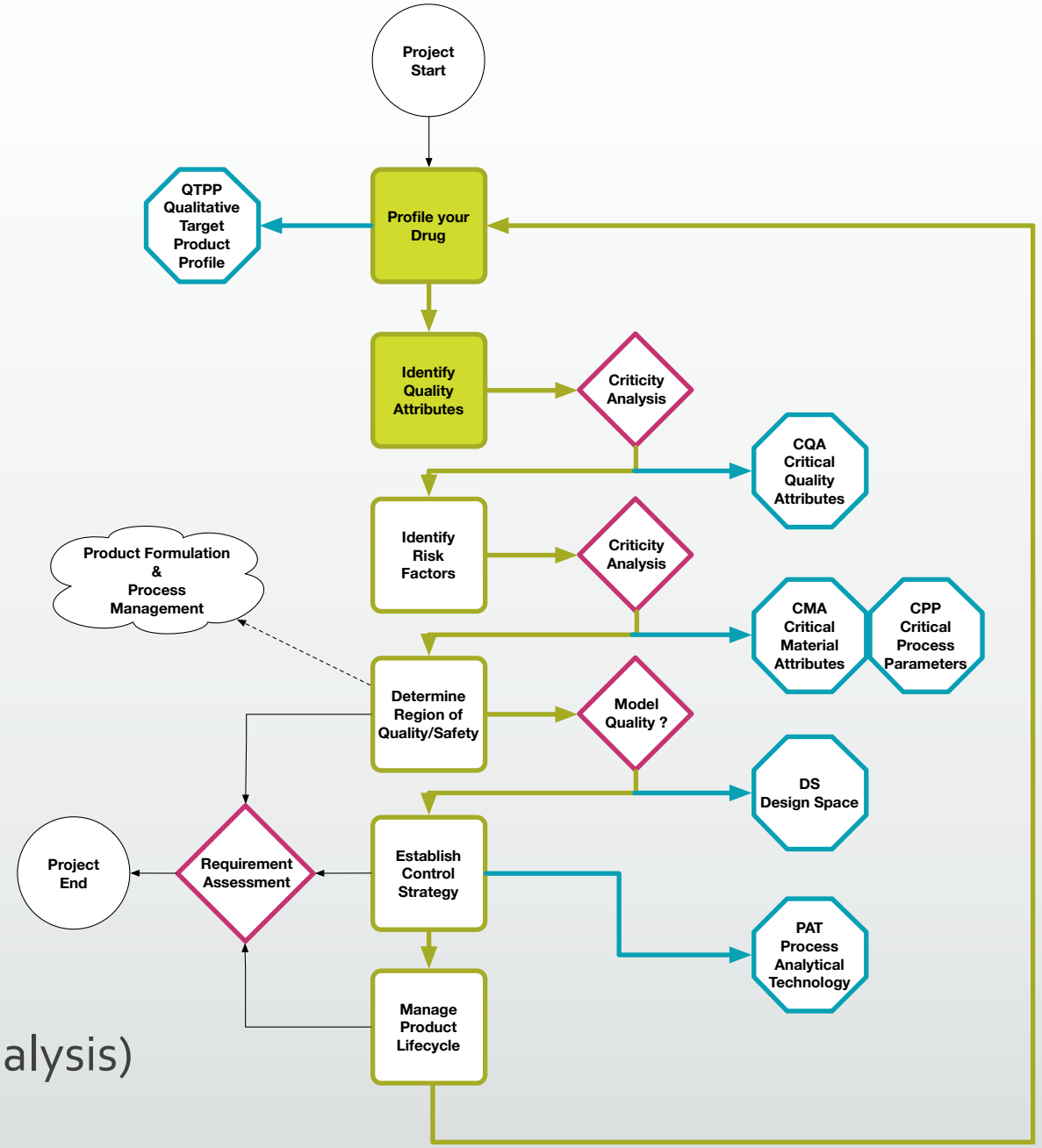
Quality Target Product Profile



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.

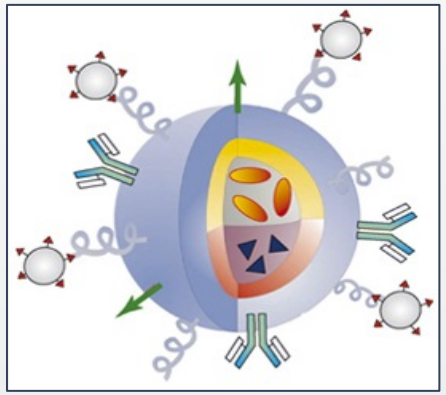
Critical Quality Attributes ?

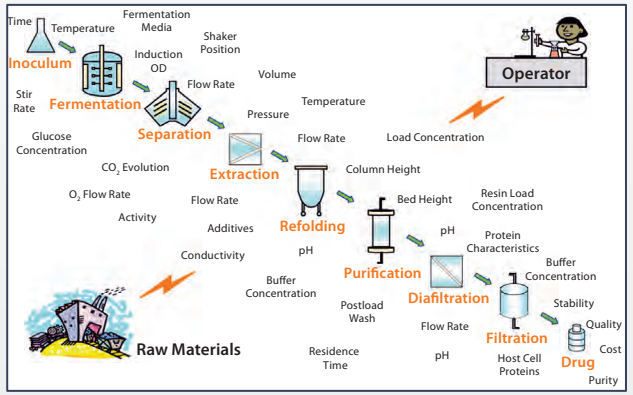


How ? Prior Risk Analysis (Failure Mode & Effect Analysis)

QbD-3: Formulation & Production Factors ?

Which are the most influent factors that could cause variability of CQA ?

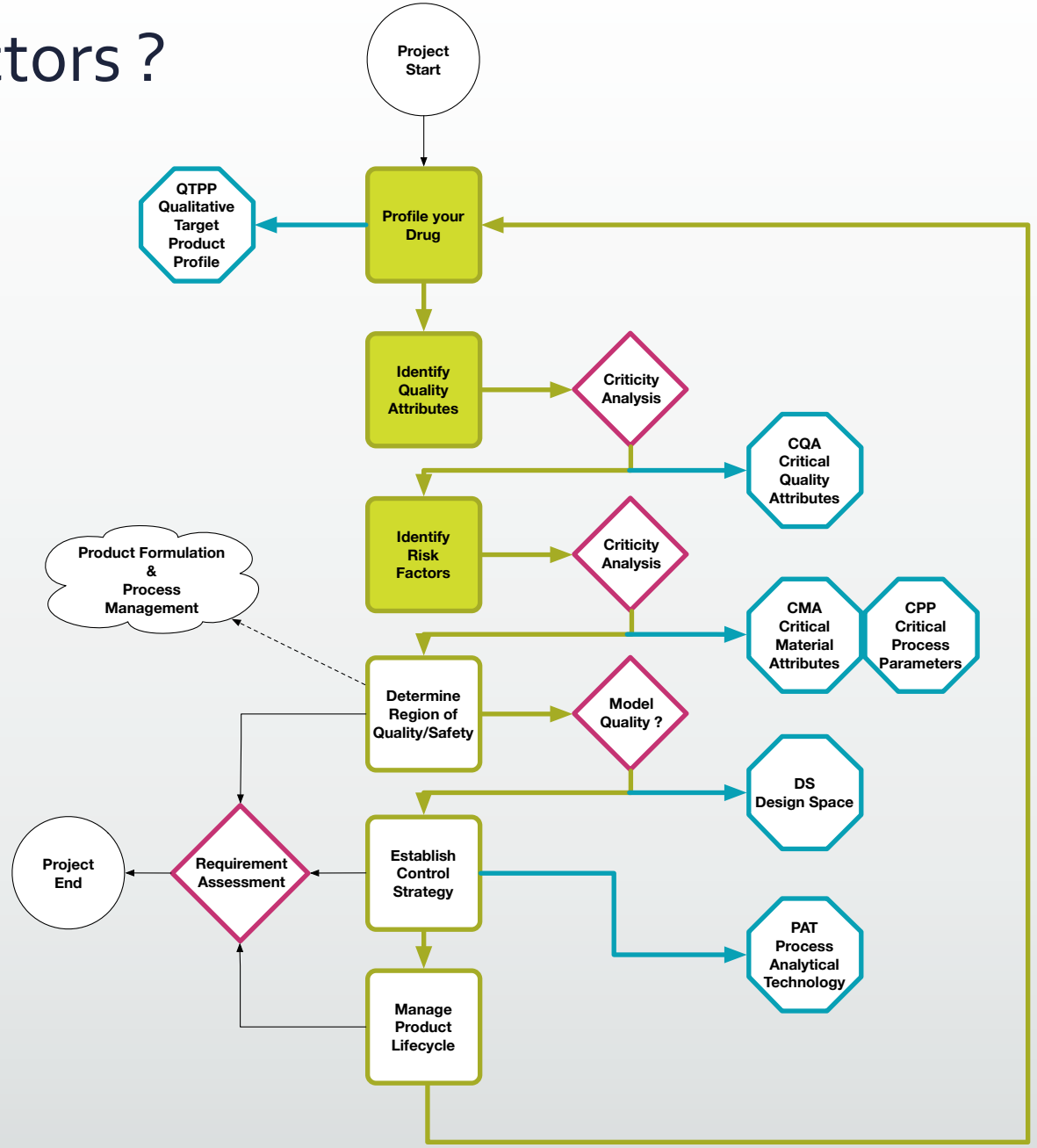




CMA
Critical Material Attributes

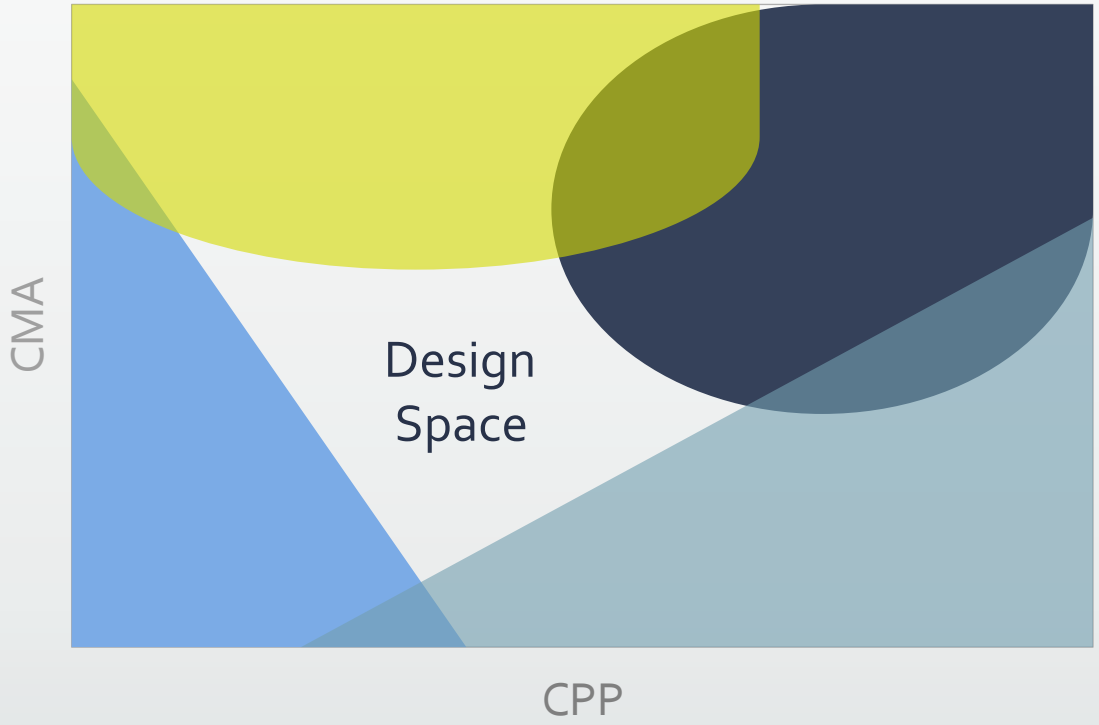
CPP
Critical Process Parameters

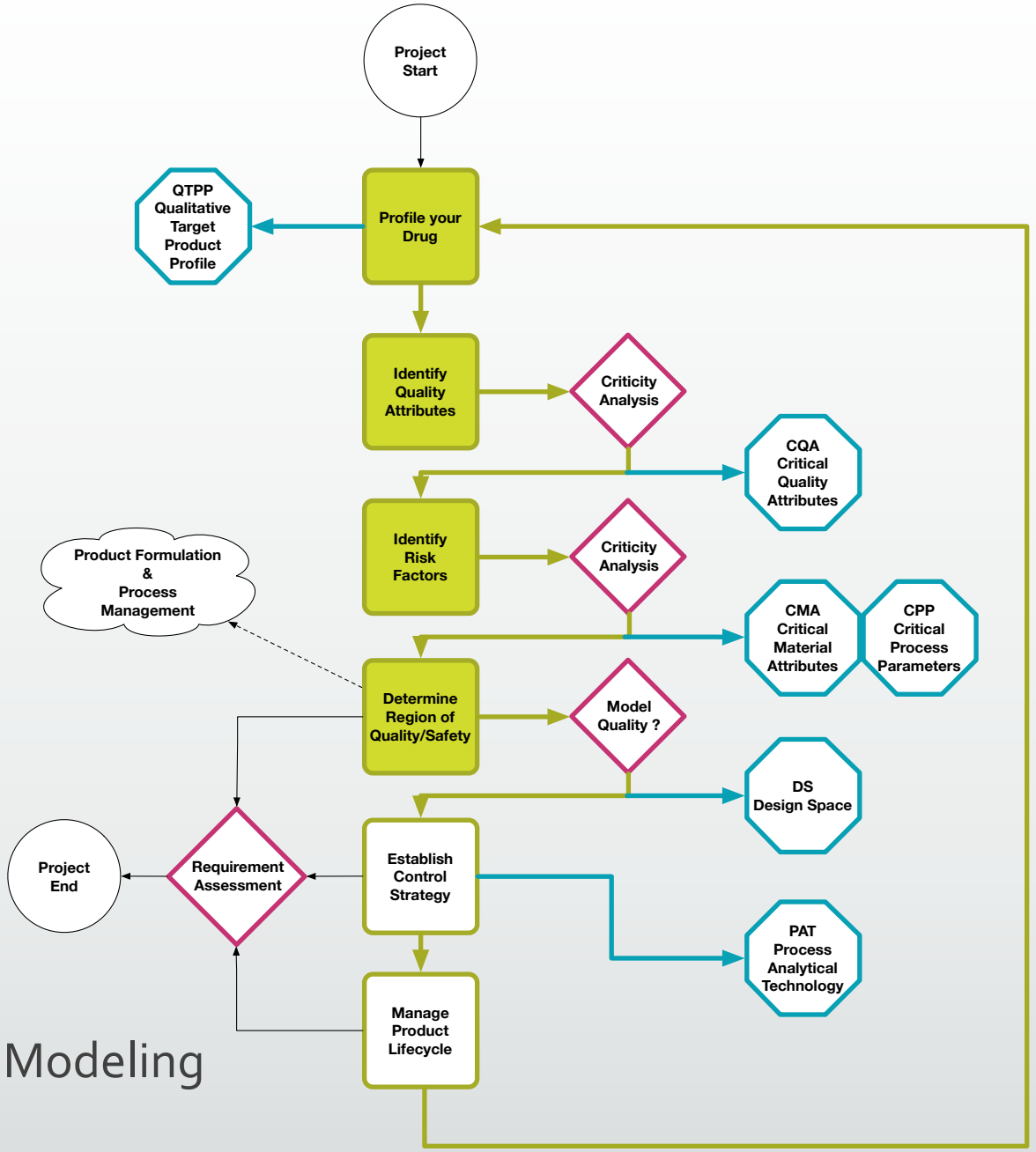
How ? Design of Experiments for Factor Screening



QbD-4: Design Space ?

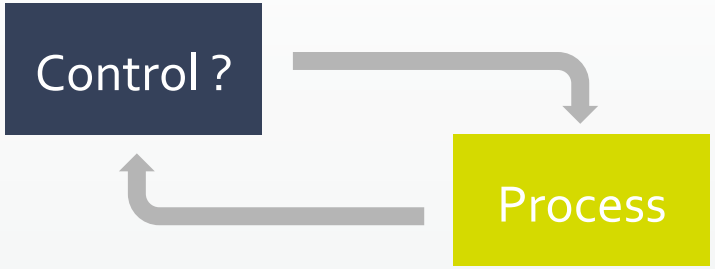
CQA = f(CMA,CPP)

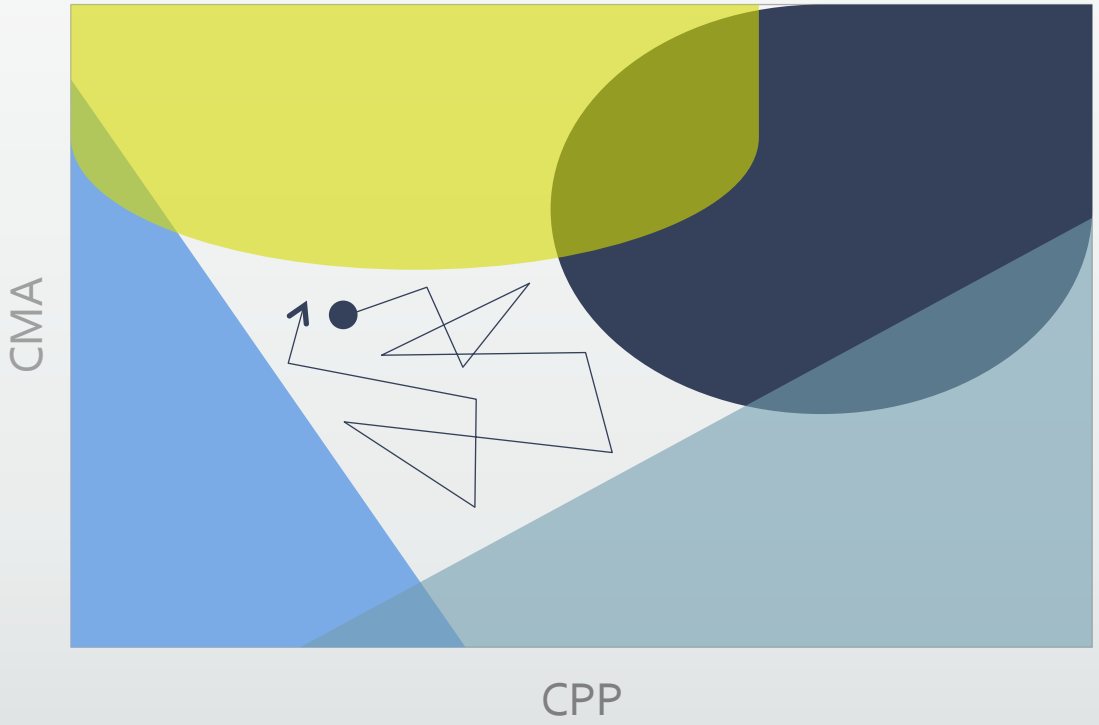


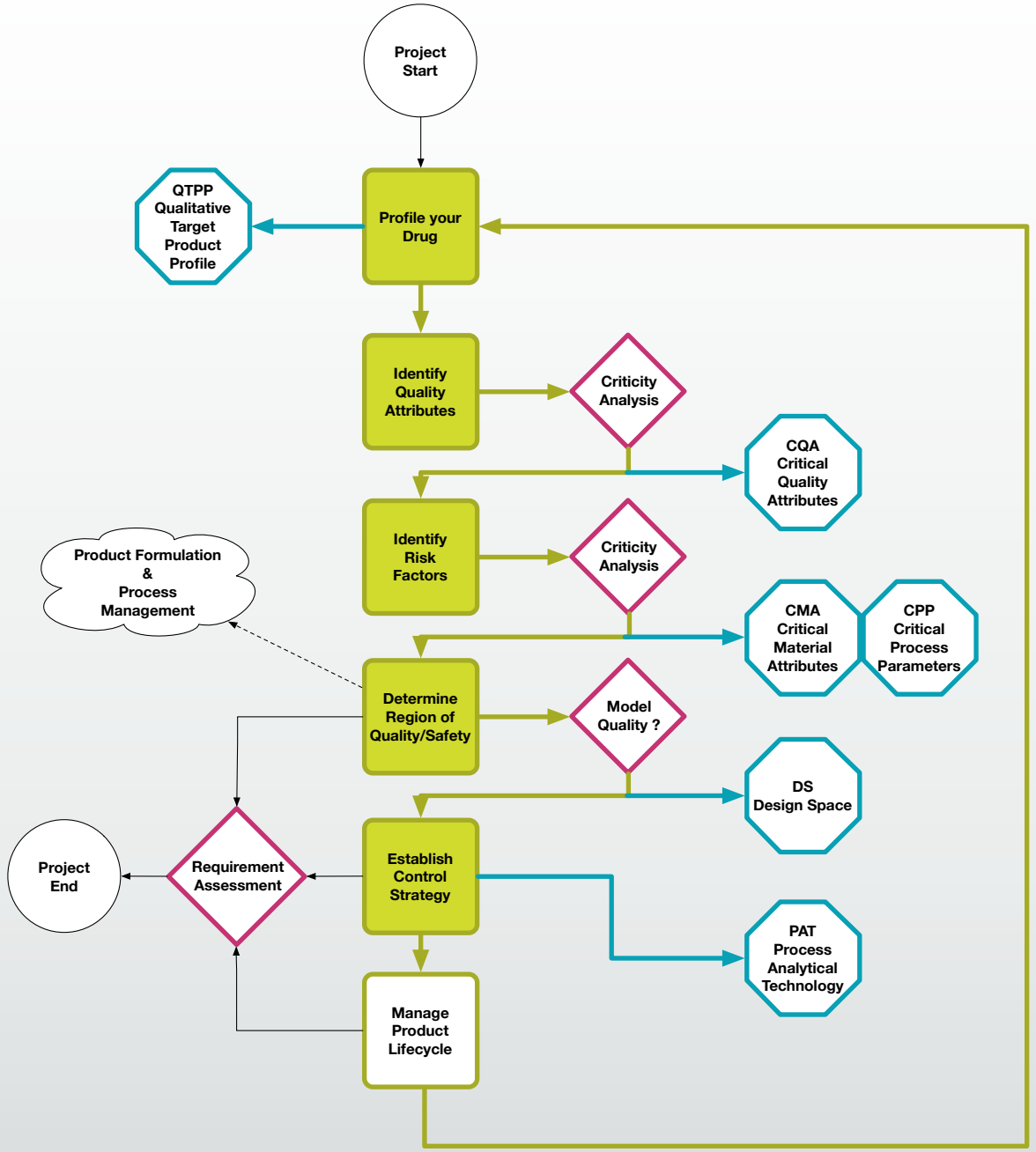


How ? Design of Experiments for Response Surface Modeling

QbD-5: Control Strategy ?

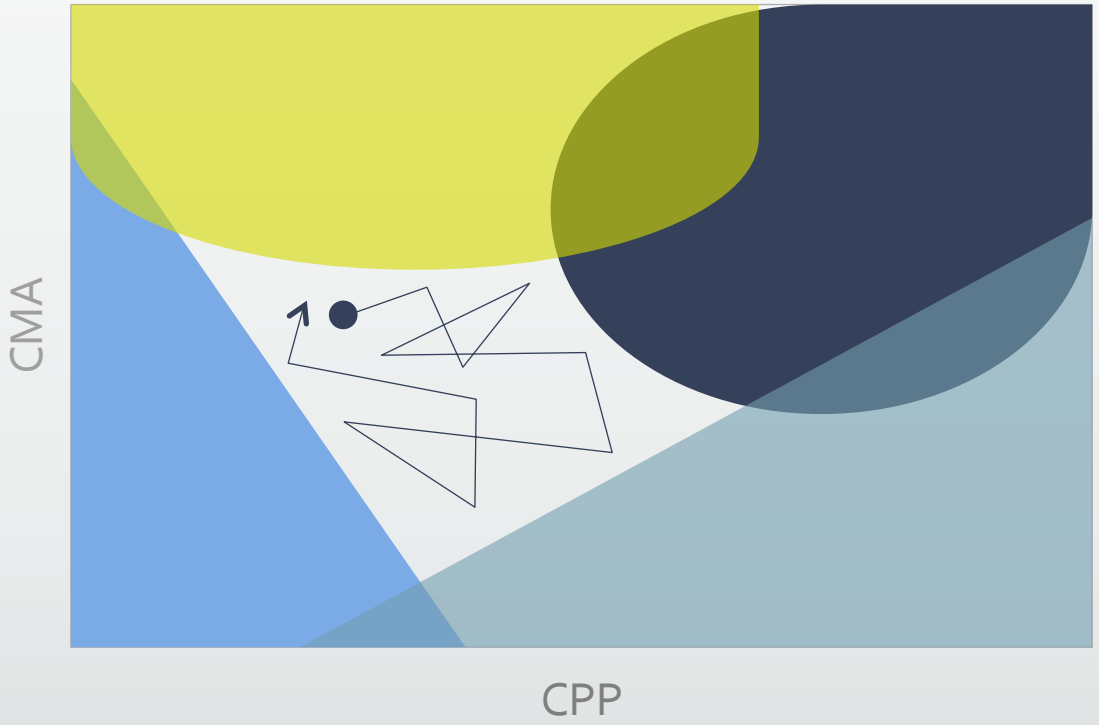


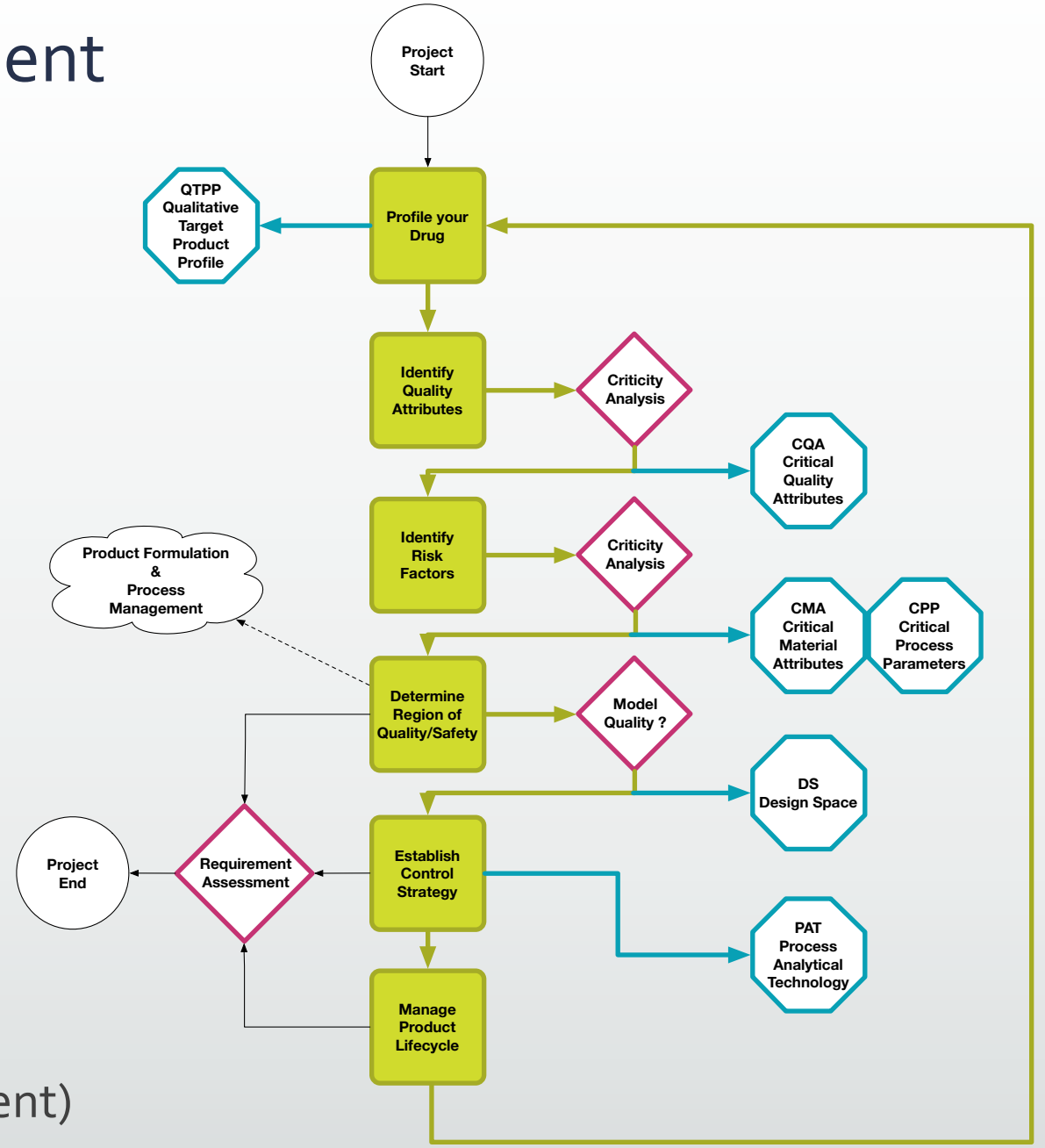




How ? Statistical Process Control

QbD-6: Product LifeCycle Management



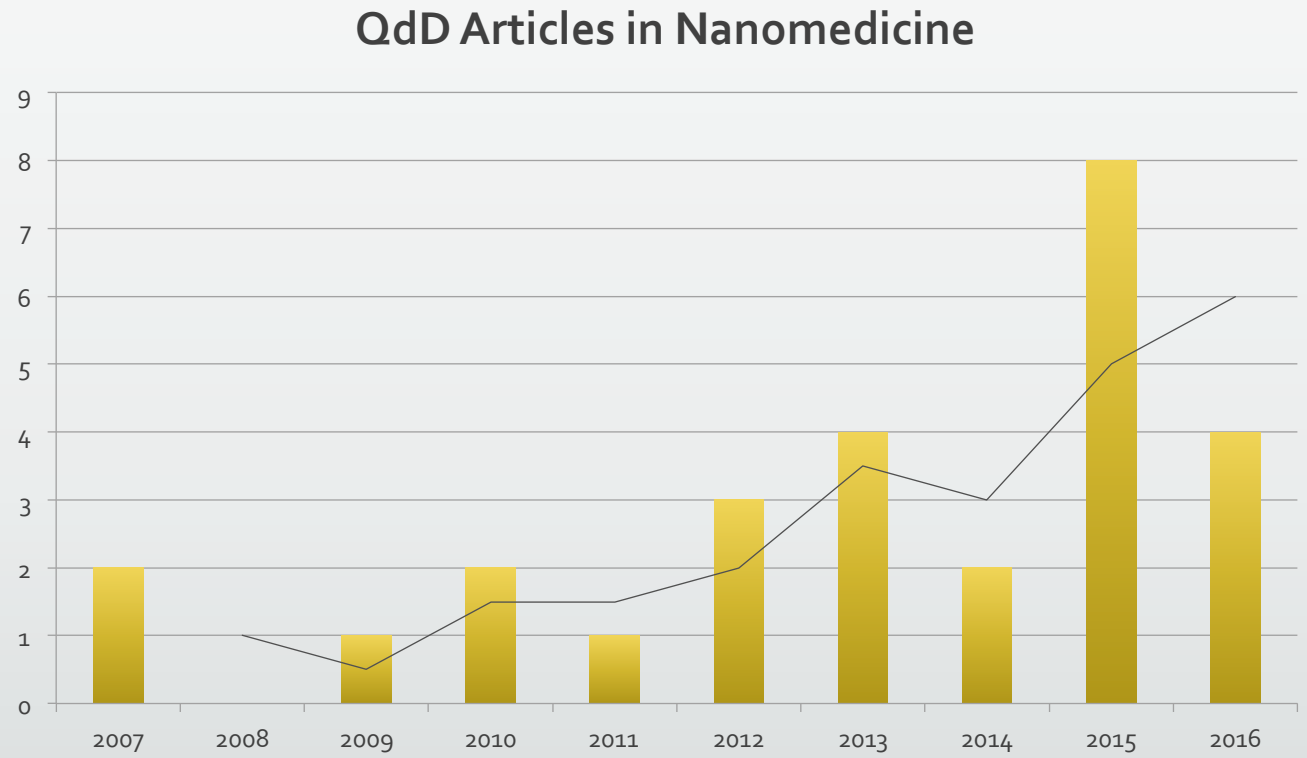


How ? PLM Methods (Product LifeCycle Management)

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



T. Bastogne, "Quality-by-design of nano-pharmaceuticals - A state of the art," Nanomedicine: Nanotechnology, Biology, and Medicine. June 2017.

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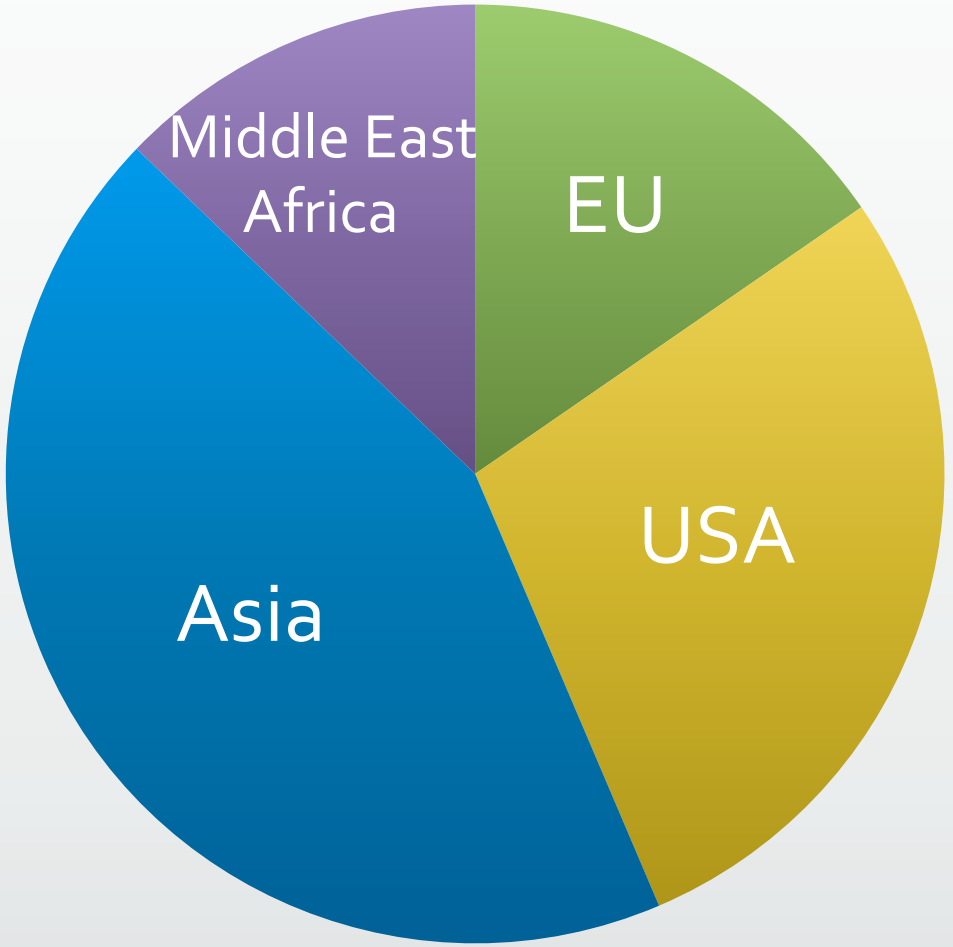
Framework Programme of the European Union

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

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

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

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

QTPP of a gel with polymeric nanoemulsified particles

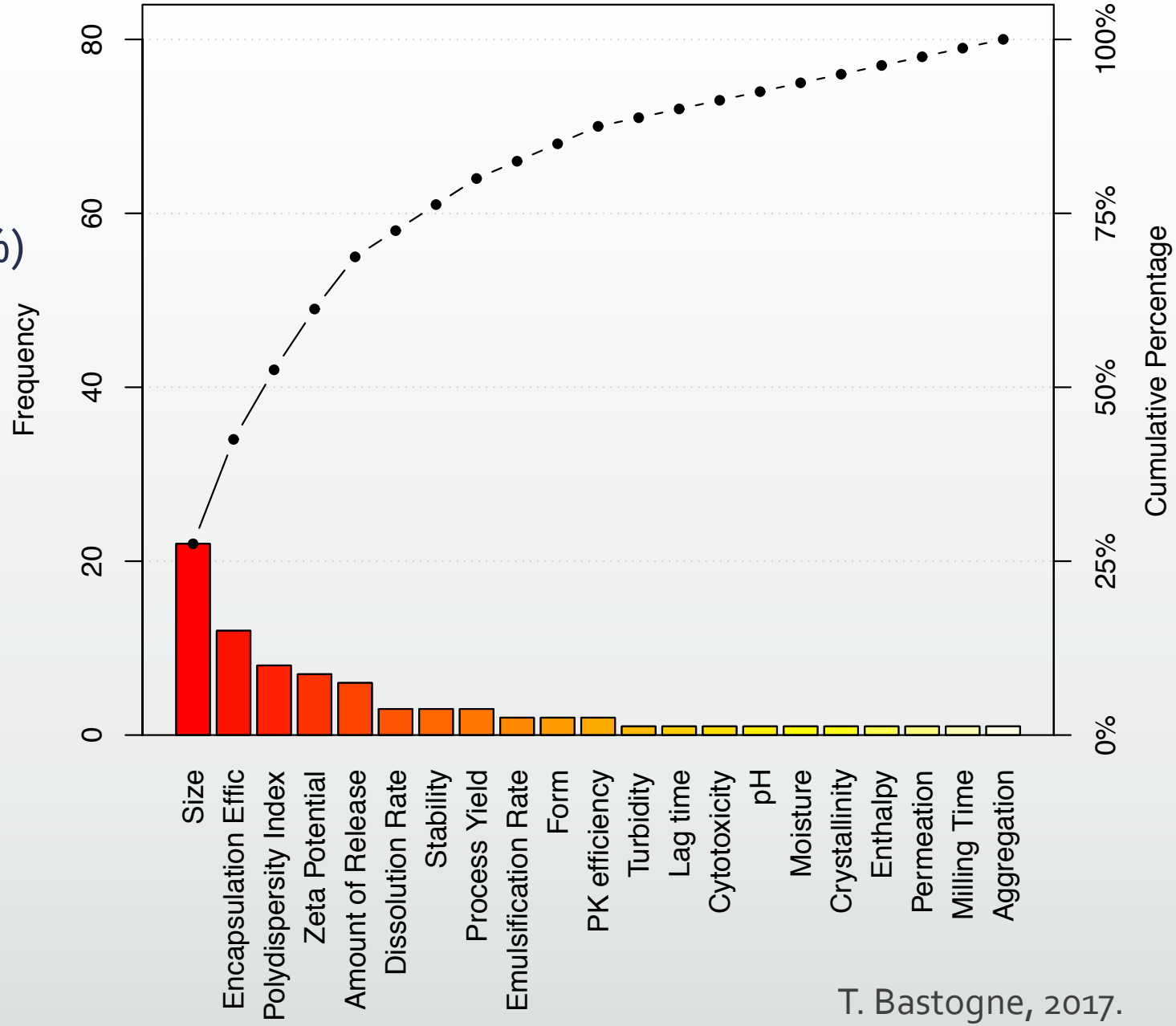
QTPP elements	Target	Justification
Dosage form	Hydrogel	Pharmaceutical equivalence requirement: same dosage form
Route of administration	Injection	Pharmaceutical equivalence requirement: same route of administration
Dosage strength	% of drug substance (% w/w)	Pharmaceutical equivalence requirement: same 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, uniformity of content, degradation products, residual solvents, dissolution, microbiological quality, pH, and rheological behavior	Pharmaceutical equivalence requirement: fulfill the same quality standards as reference-listed drug product
Container closure system	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	Vials or prefilled syringes, similar with reference-listed drug product, acceptable for the patient
Alternative methods of administration	No	None are listed on reference drug product labeling

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

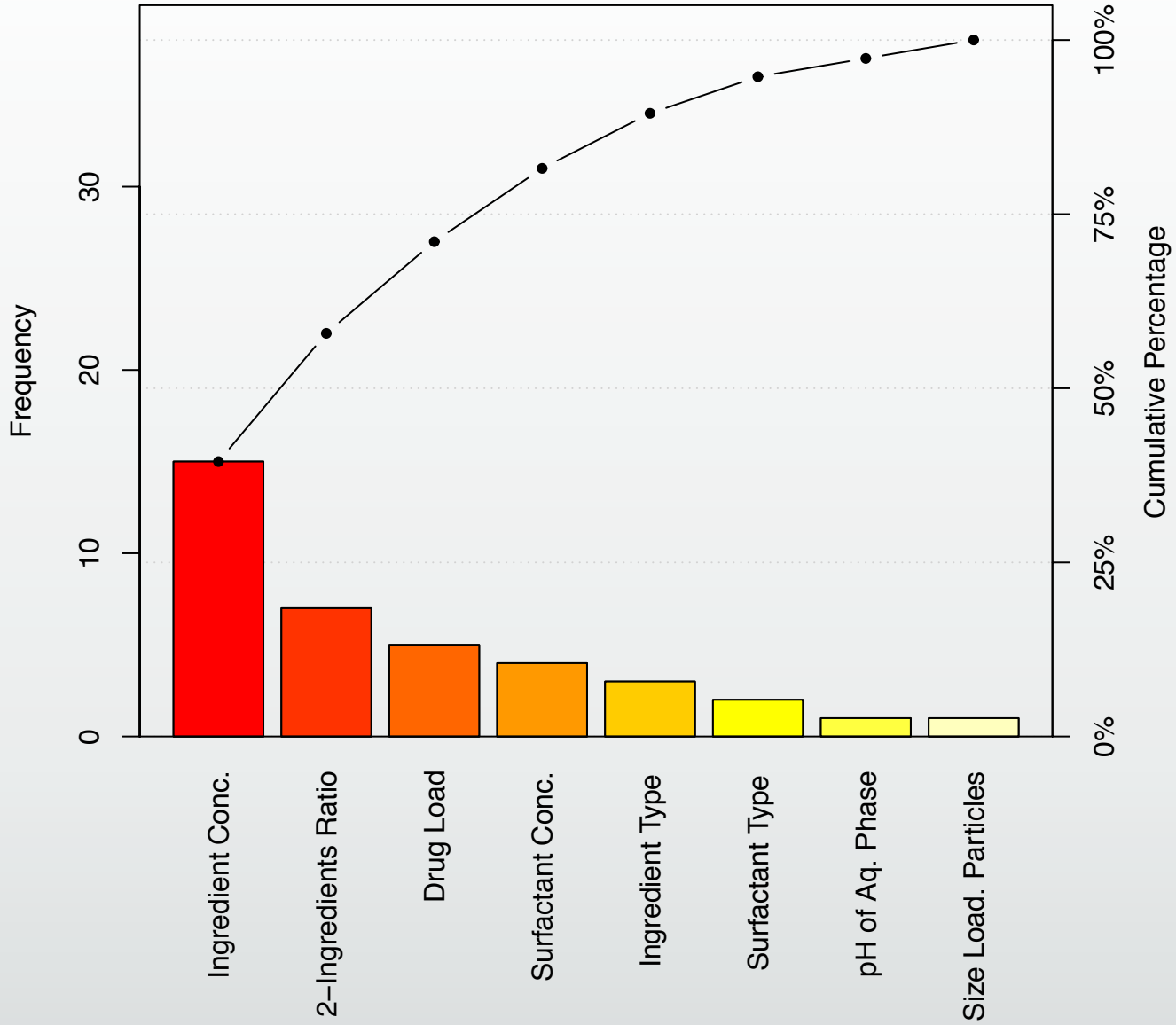


T. Bastogne, 2017.

3) CMA Specification

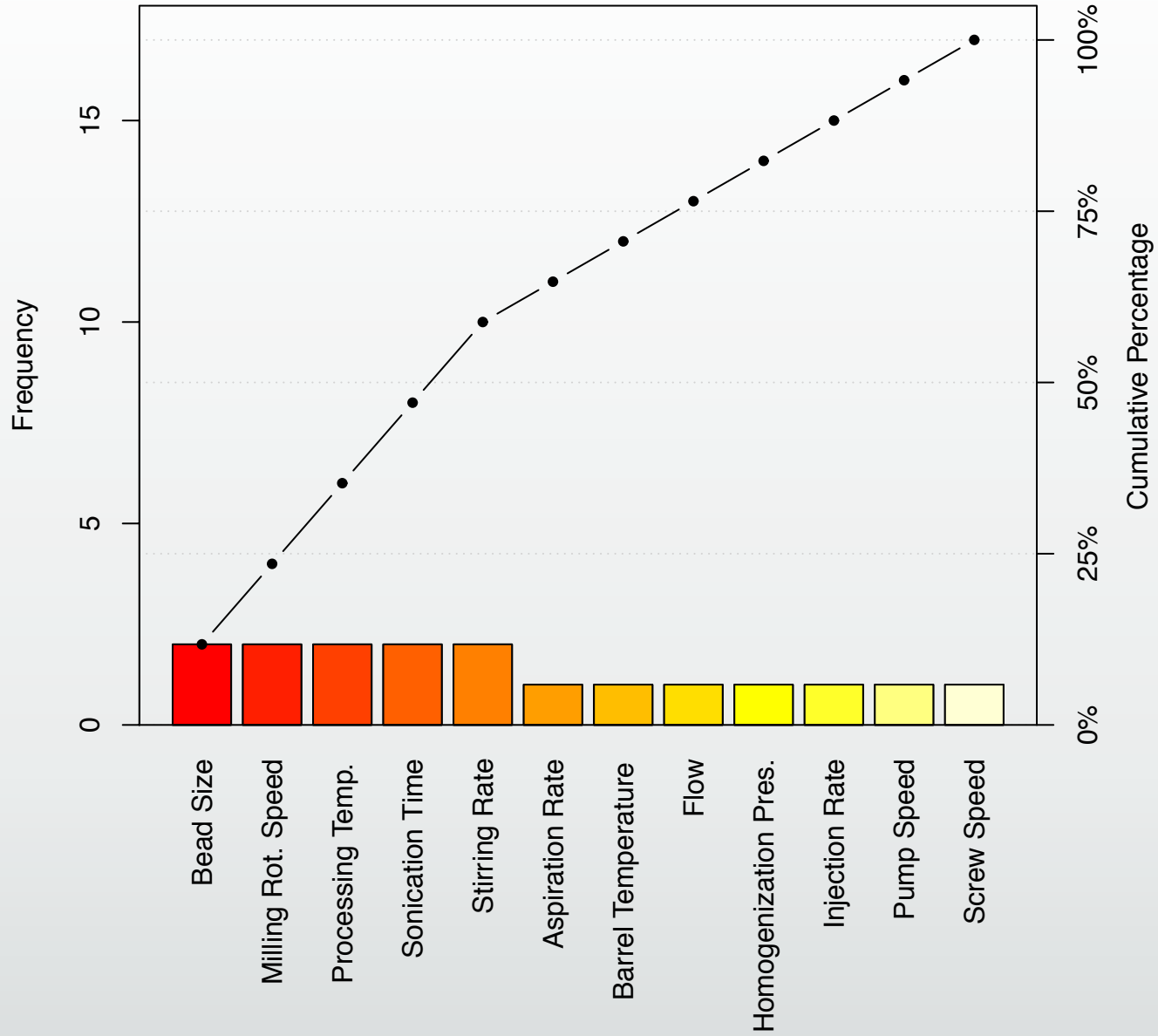
6 Criticial Material Attributes > 90%

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

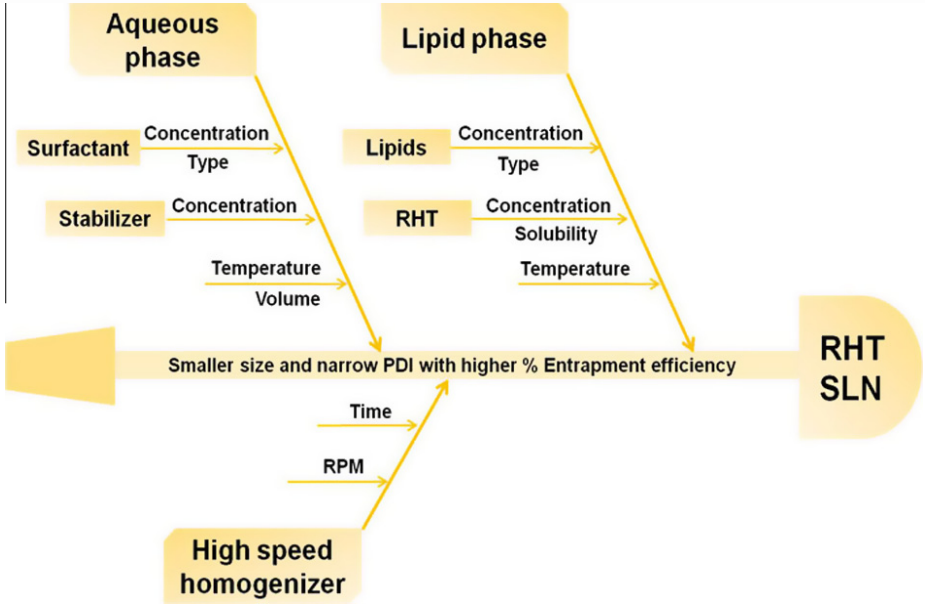


Fig. 1. Ishikawa diagram illustrating CPP affecting on CQA of RHT SLN.

B. Shah et al.,2015

Table 1
Initial risk assessment for ACE-NLCs.

Drug product CQAs	Risk estimation matrix							
	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, Low risk parameter.

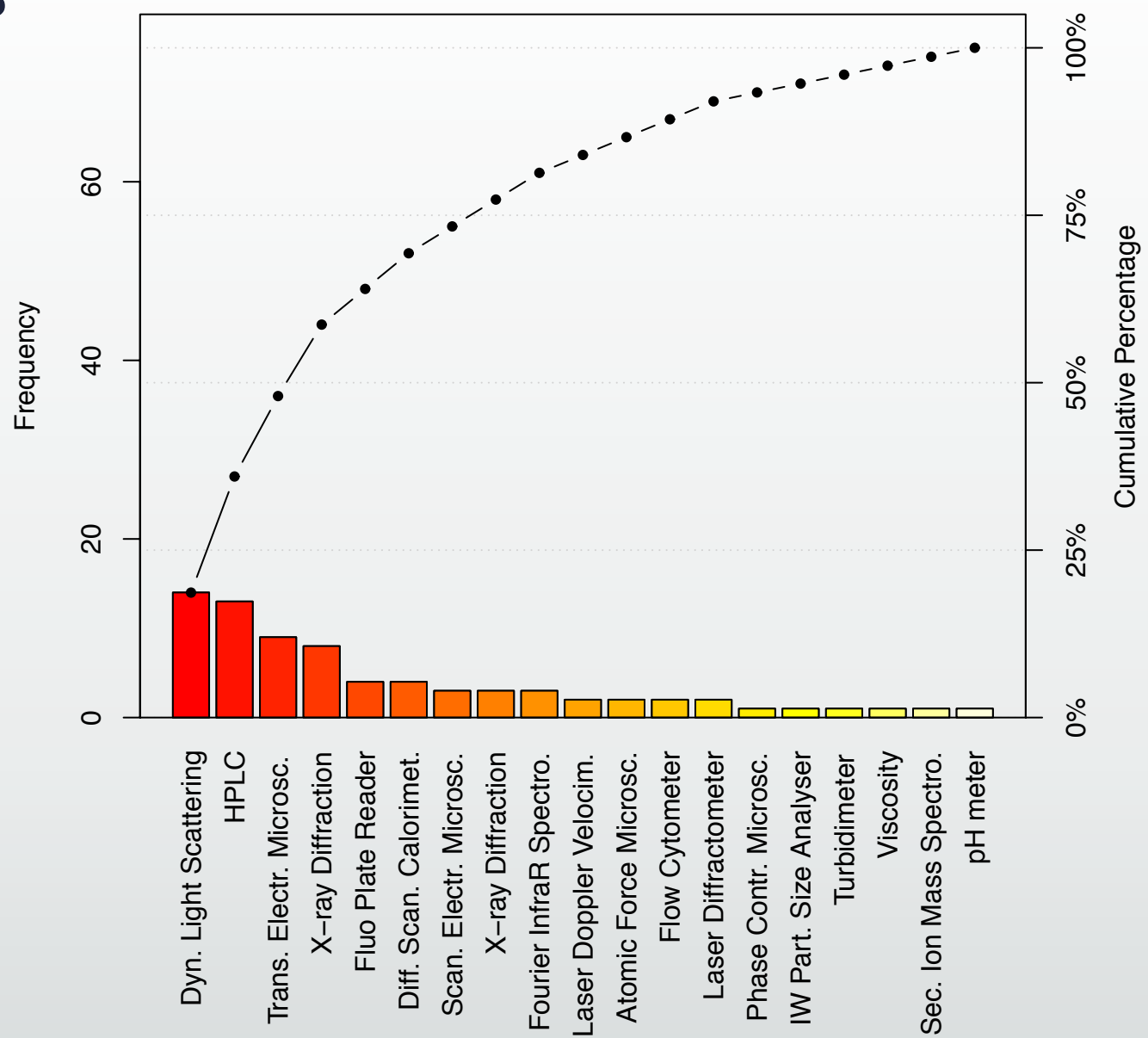
Criticity = Severity x Frequency

N.K. Garg et al., 2017

Measurement Technologies

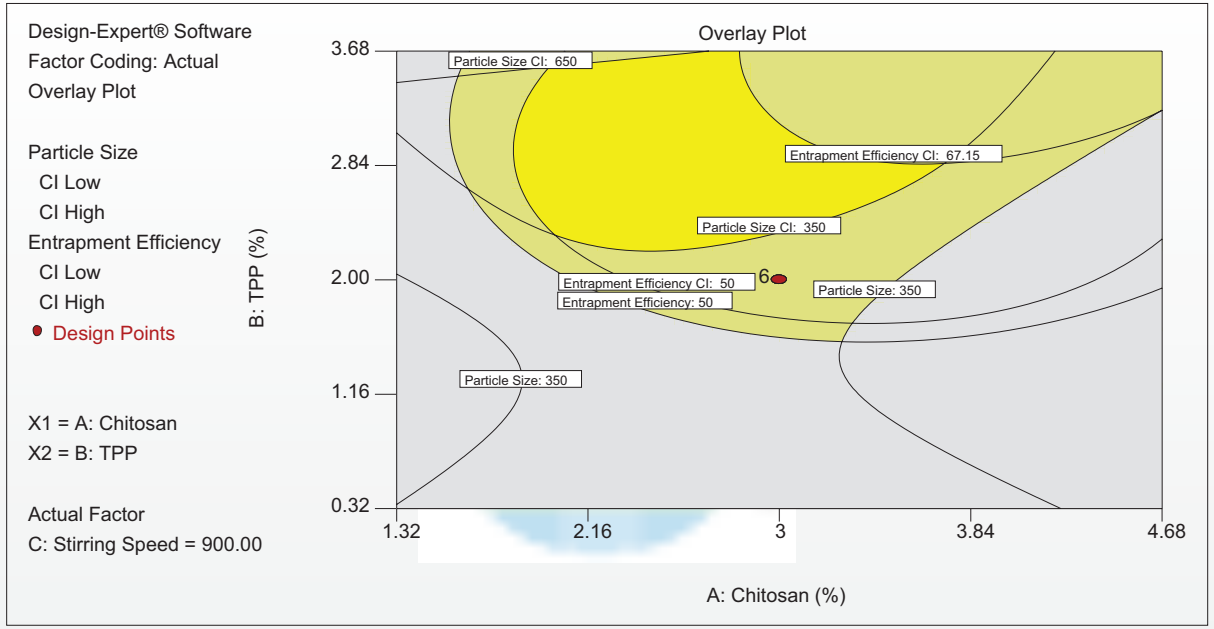
4 mian measurement techno. > 50%

1. Dyn. Light Scaterring
2. HPLC
3. Trans. Electro. Microscopy
4. X-Ray Diffraction



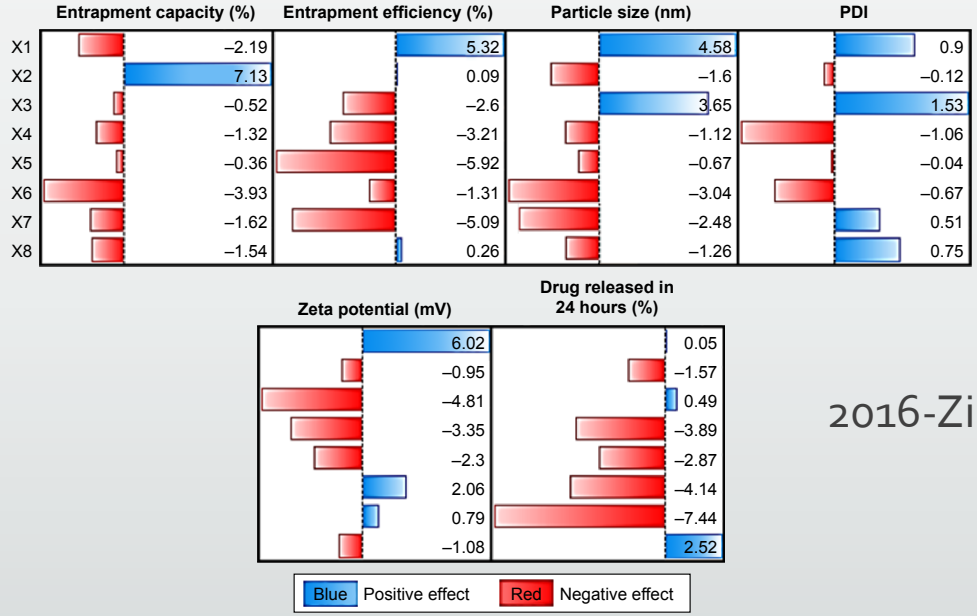
Design of Experiments

- 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

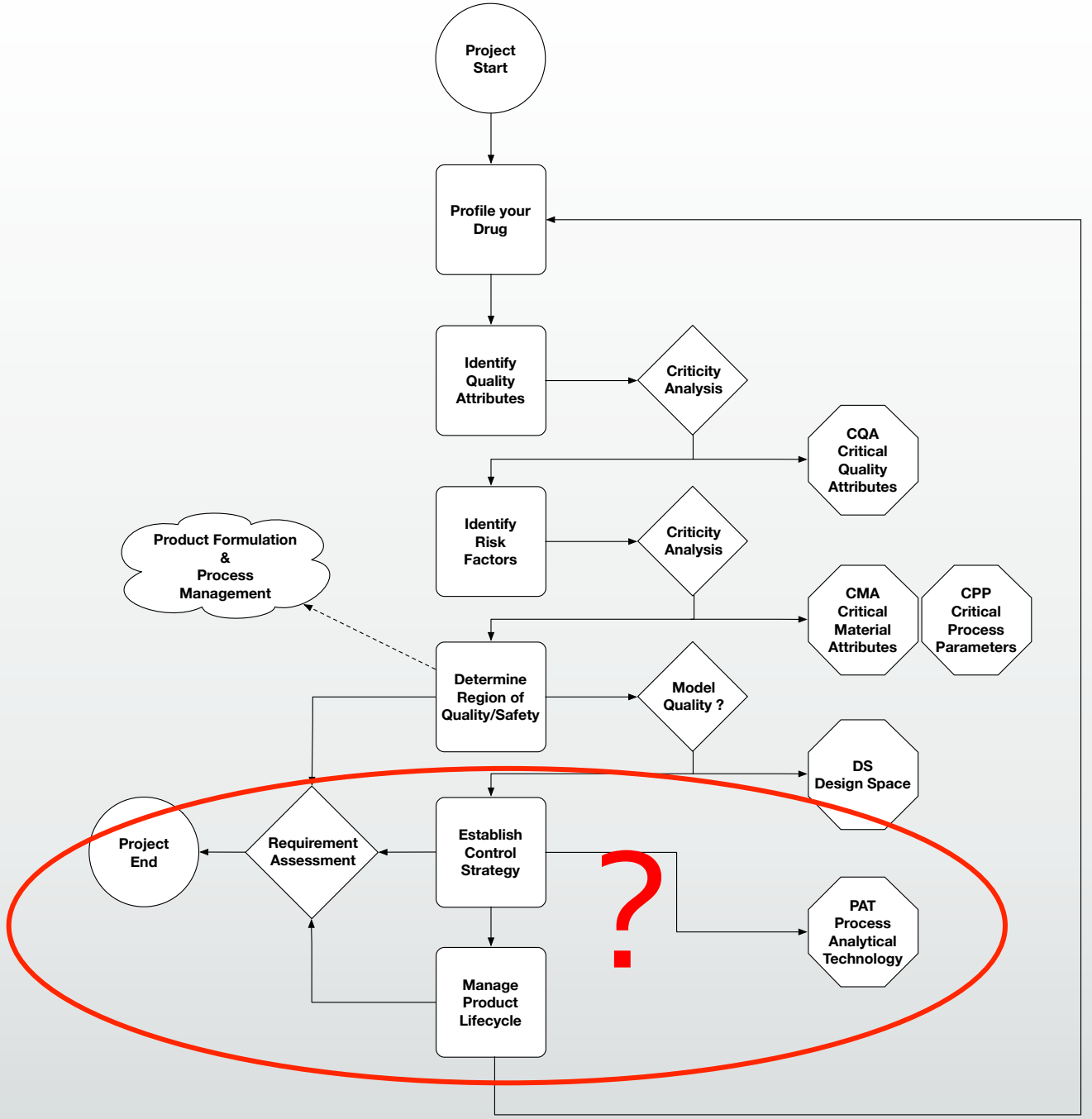
2015-Shirsat



2016-Zidan

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

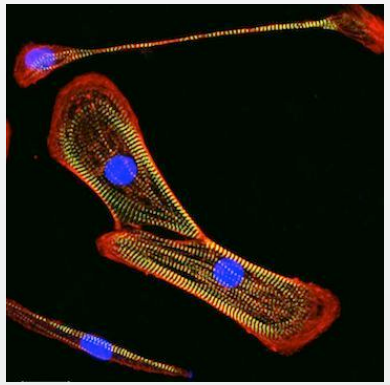
- The Quality-by-Design approach is more and more adopted in the *nano-community* mainly in India and USA.
- Nevertheless, some important parts, e.g. control strategy & quality management, are still ignored.
- Statistical tools exist but they are not always used correctly → educational effort is needed.
- 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**[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).

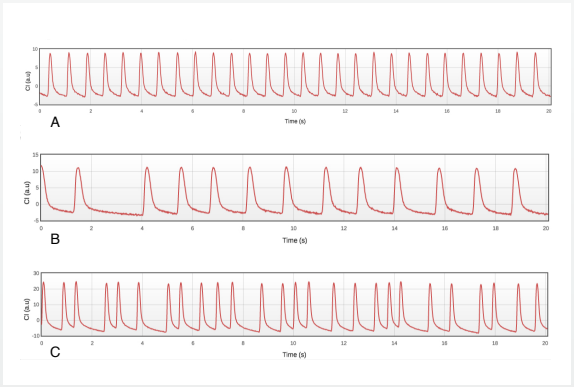
Multi-Electrode Arrays
Impedance-based Assays
Patch Clamp

+

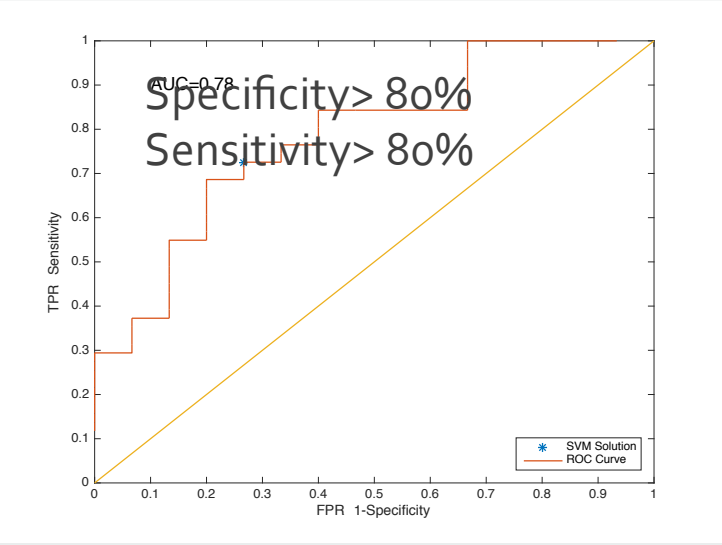


iPSC
human-iPSC-Derived
Cardiomyocites

+



Signal Processing
Machine Learning



1. CiPA: Comprehensive in vitro Proarrythmia Assay
2. 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.

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)

[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.
[4] P. Guyot, L. Batista, E. Djermoune, J.-M. Moureaux, L. Doerr, M. Beckler, and T. Bastogne, "Compar- ison of compression solutions for impedance and field potential signals of cardiomyocytes," in Proc of the 44-th Annual Conf. Computing in Cardiology, (Rennes, France), September 24-27 24-27 2017.
[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 ipsc-cardiomyocytes," 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 ?