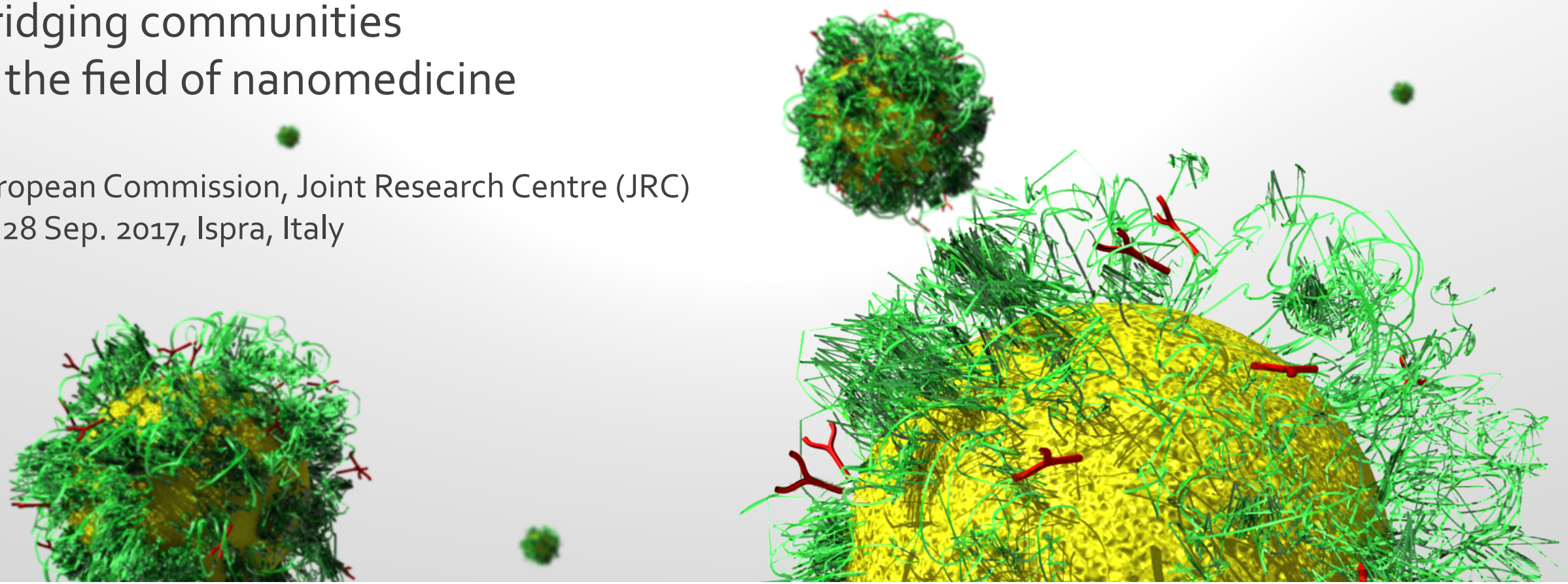
Bridging communities
in the field of nanomedicine

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

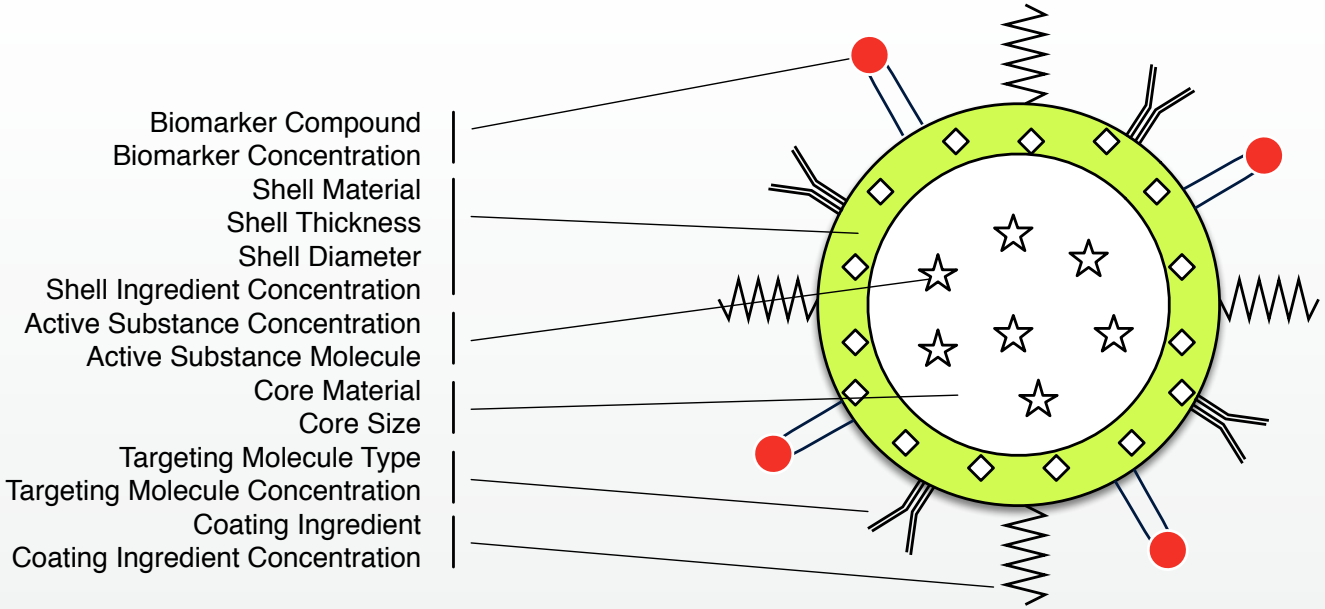


# Quality-by-Design of Nanopharmaceuticals. A State of the Art

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

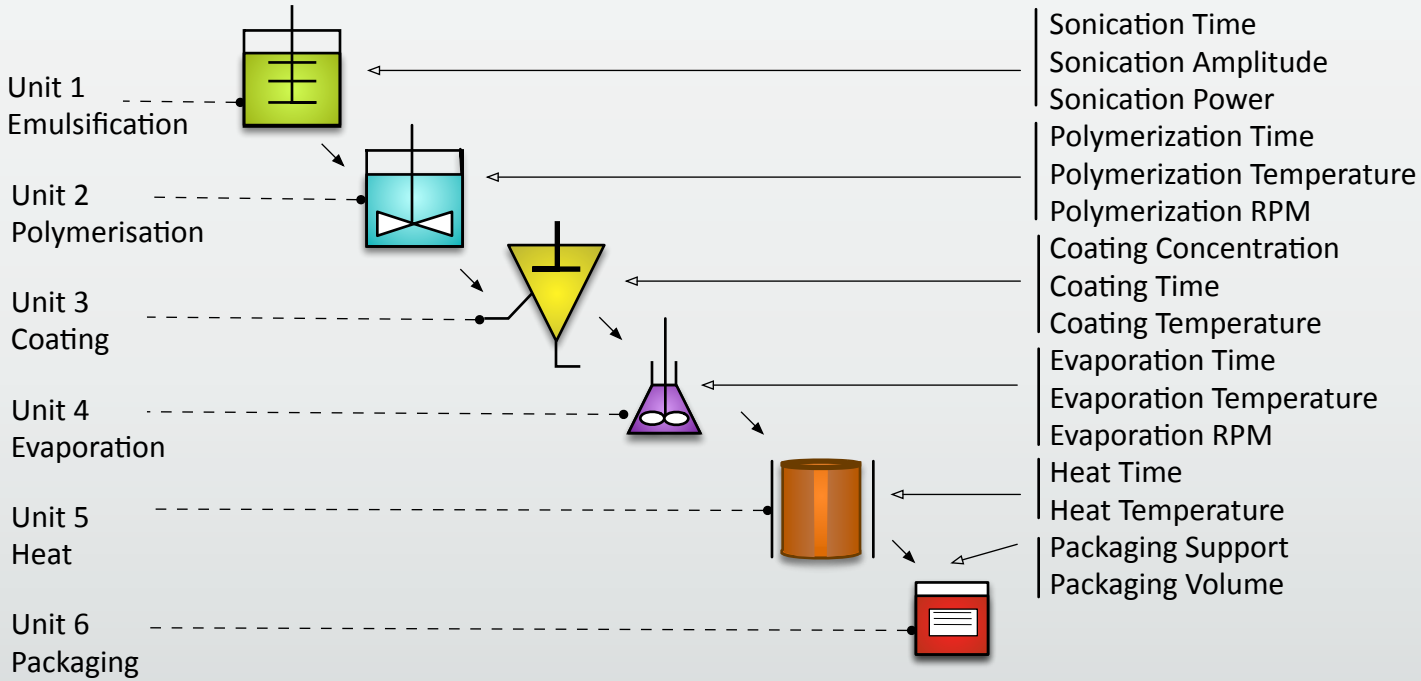
# Contents

1. QbD in Theory
2. QbD in Practice (2007-2017)
3. One perspective…




7 compounds
2 parameters
3 tested values

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

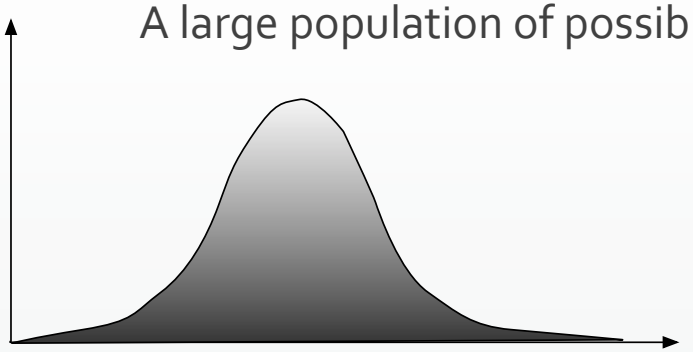



6 production units
3 parameters
3 tested values

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



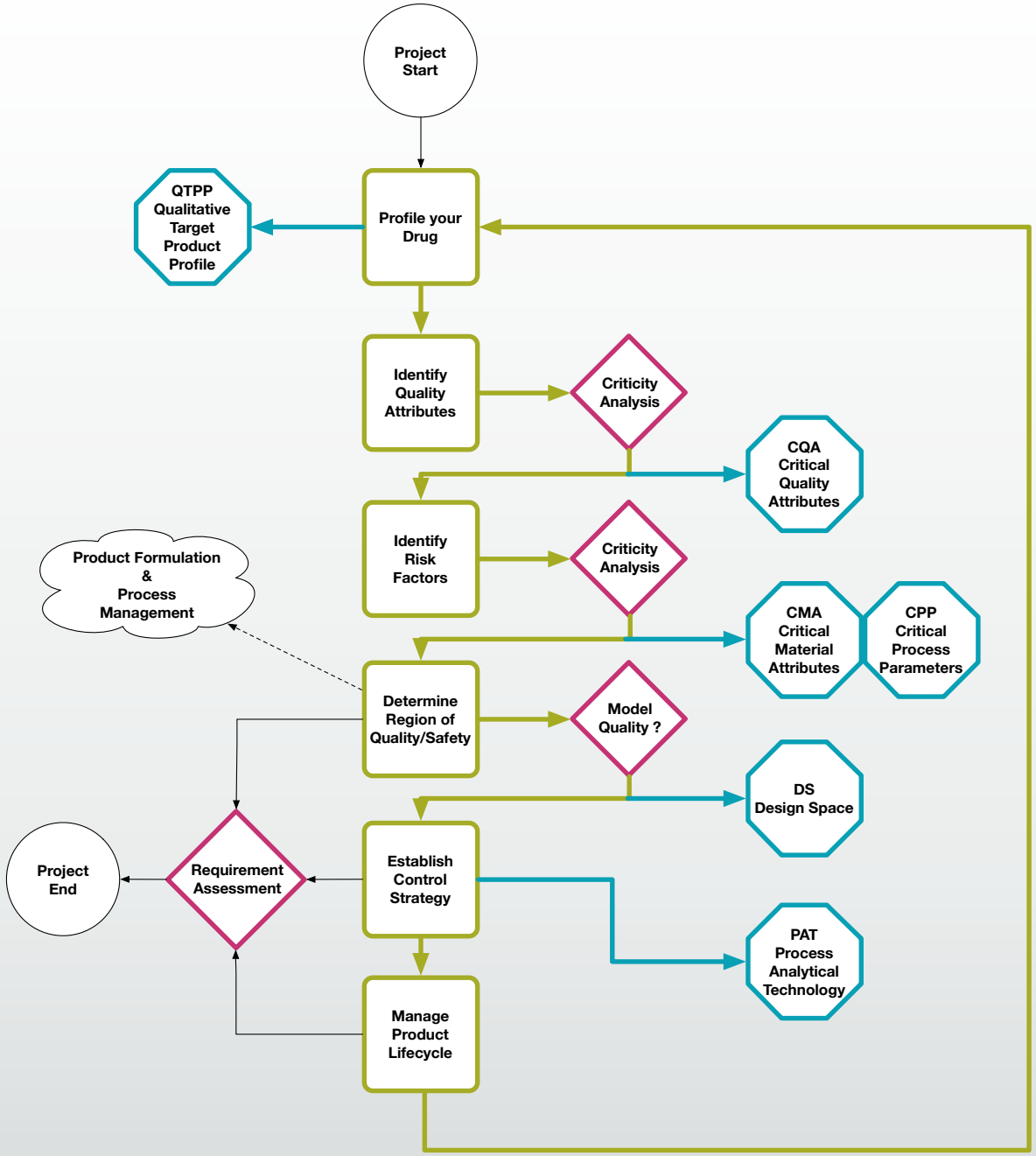

- Aeronautics & Automative Industries : Total Quality Management, Design for Six-Sigma
- FDA officials realized that biologics and drugs could also stand to benefit from QbD.
- **Concept paper** on 21st Century Good Manufacturing Practices.
- FDA produced a **guidance** document : « Pharmaceutical cGMPs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

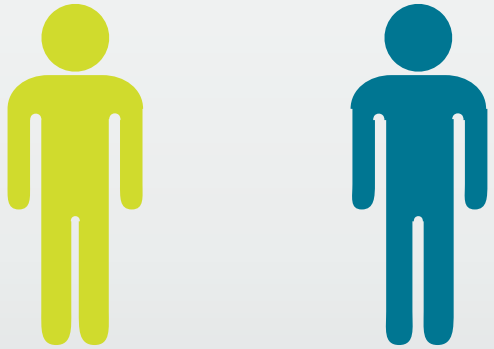
- 6 main tasks
- 6 main deliverables
- 4 go / no go tests



# QbD LifeCycle

A risk-based project management :

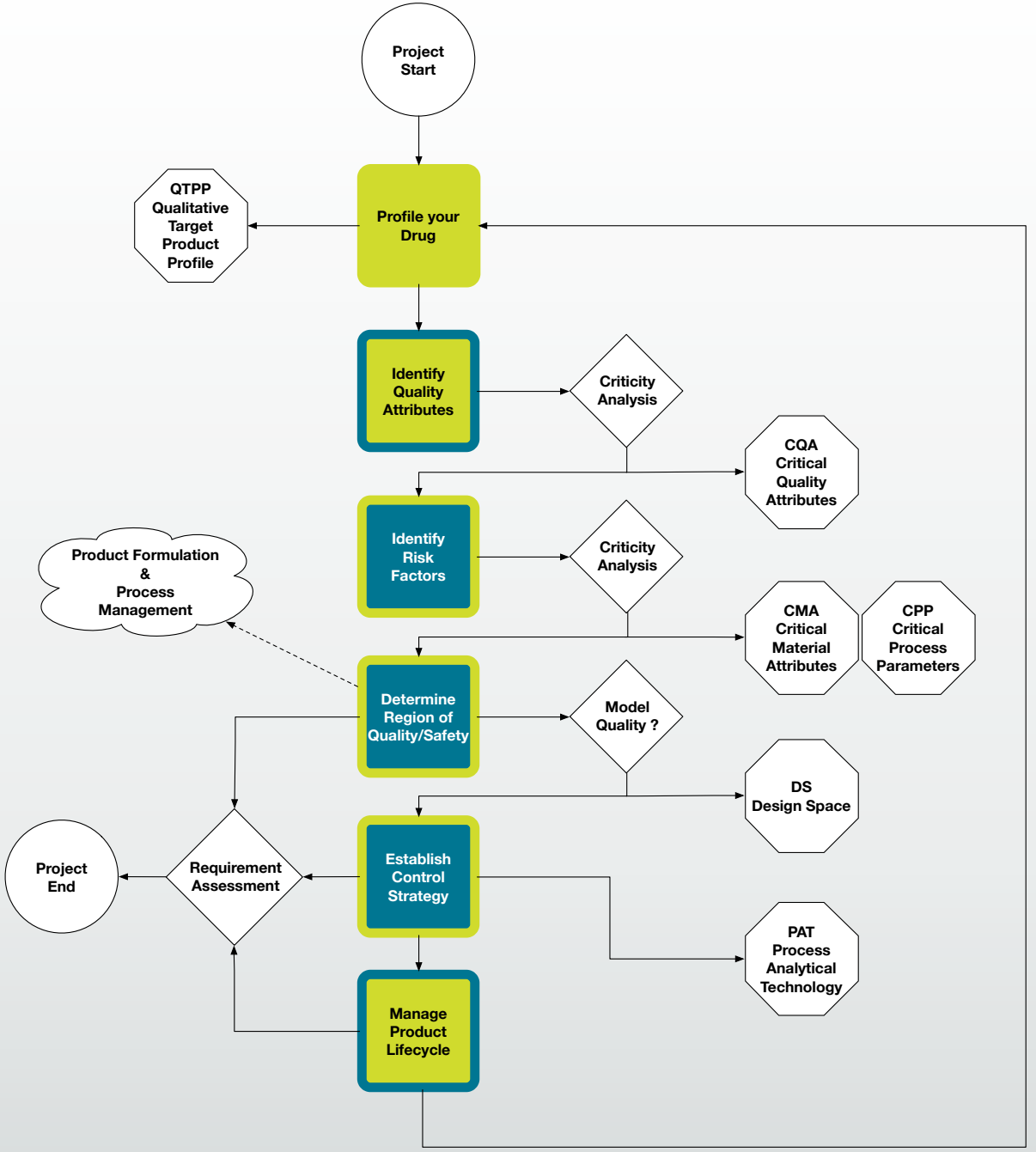
- 6 main tasks
- 6 main deliverables
- 4 go / no go testing



Life Scientist



Data Scientist

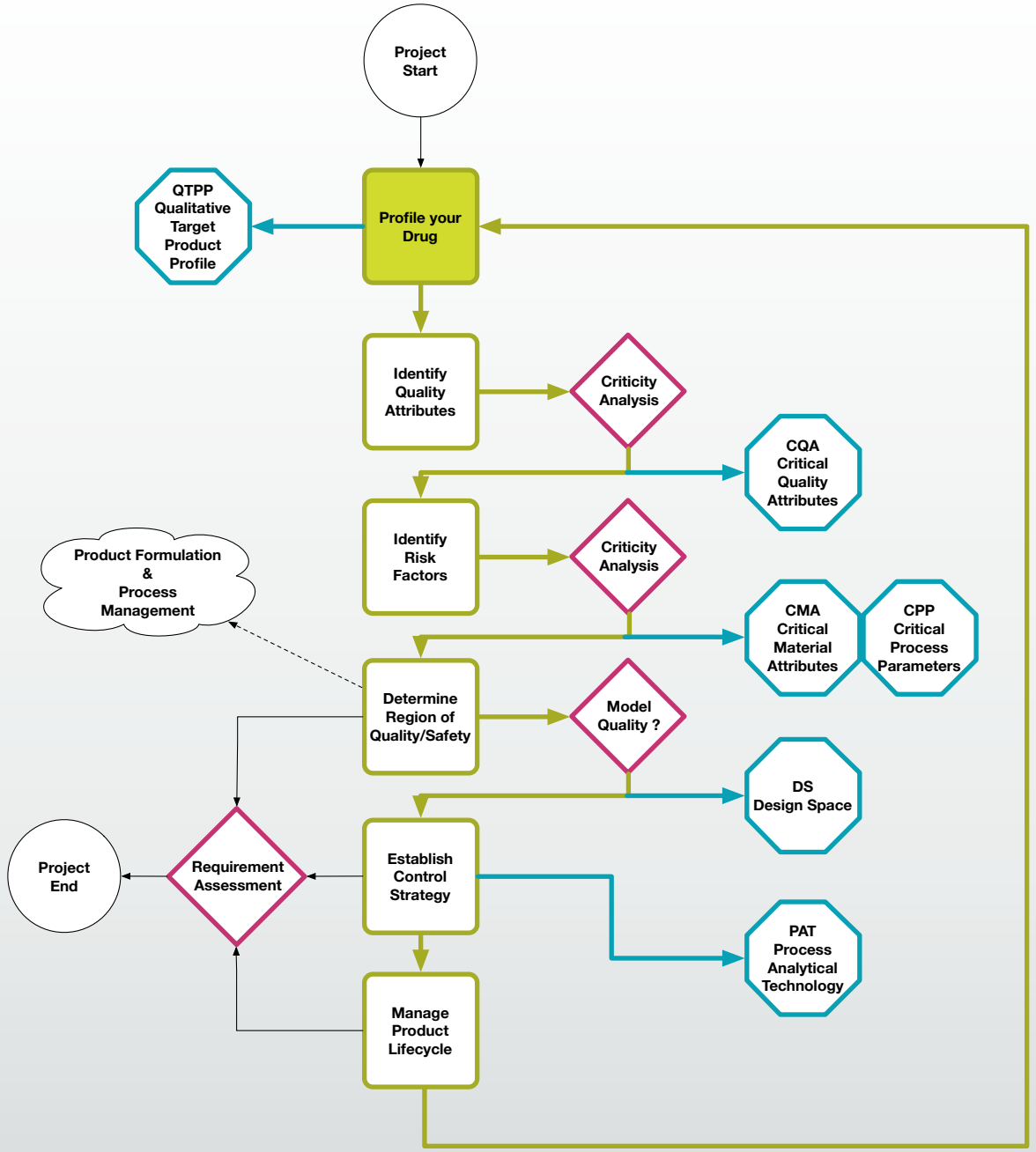


# QbD-1: Profile your Nano

- ✓ 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

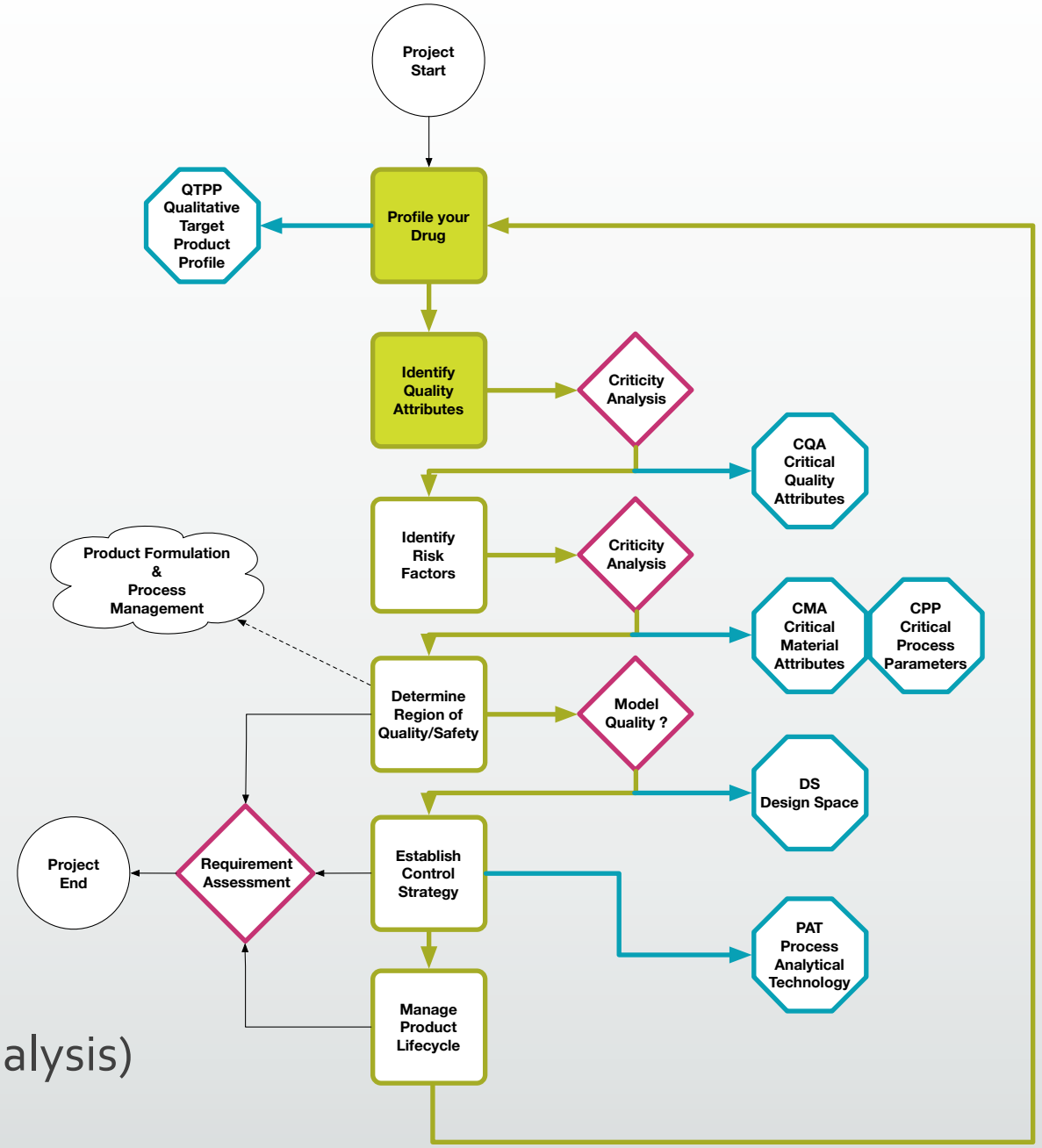


# QbD-2: Quality Attributes ?

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.



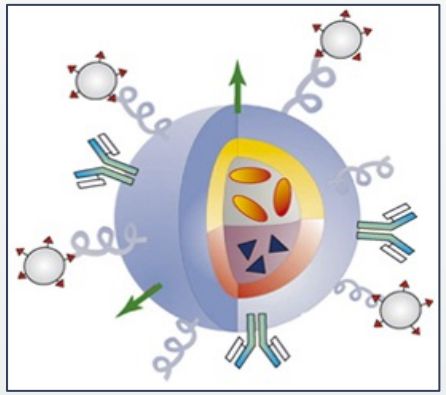

**Critical Quality Attributes ?**

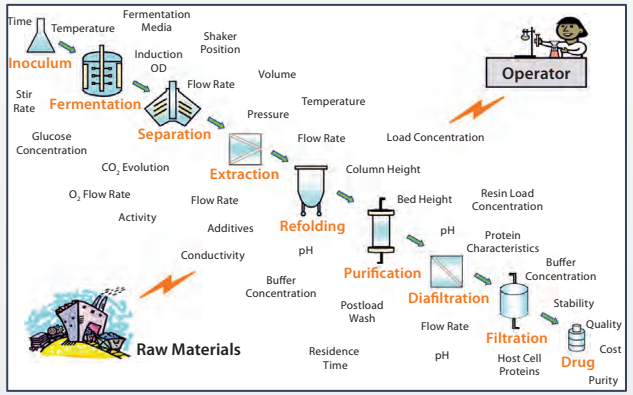



**How ?** Prior Risk Analysis (Failure Mode & Effect Analysis)

# QbD-3: Formulation & Production Factors ?

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

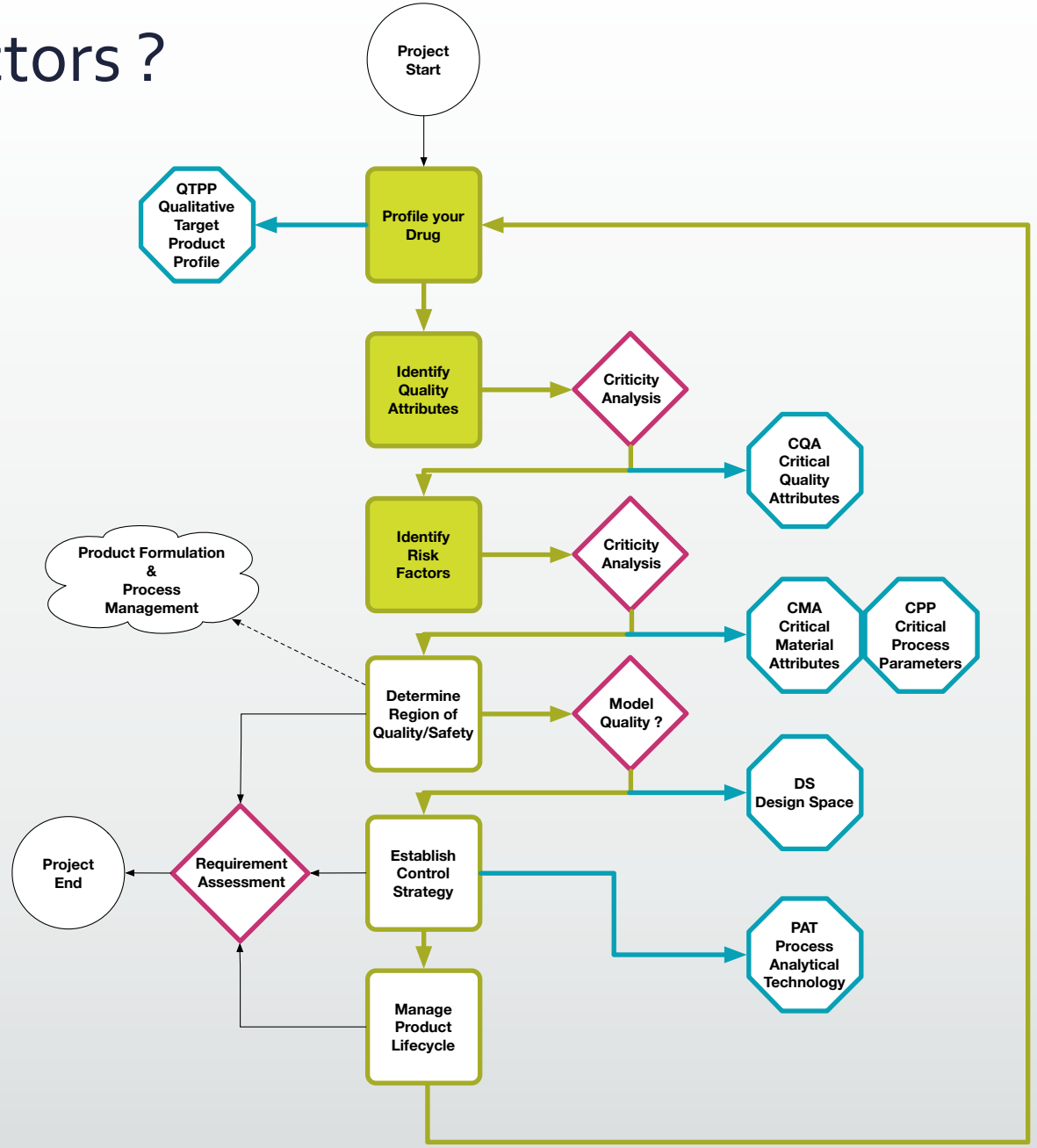





CMA
Critical Material Attributes

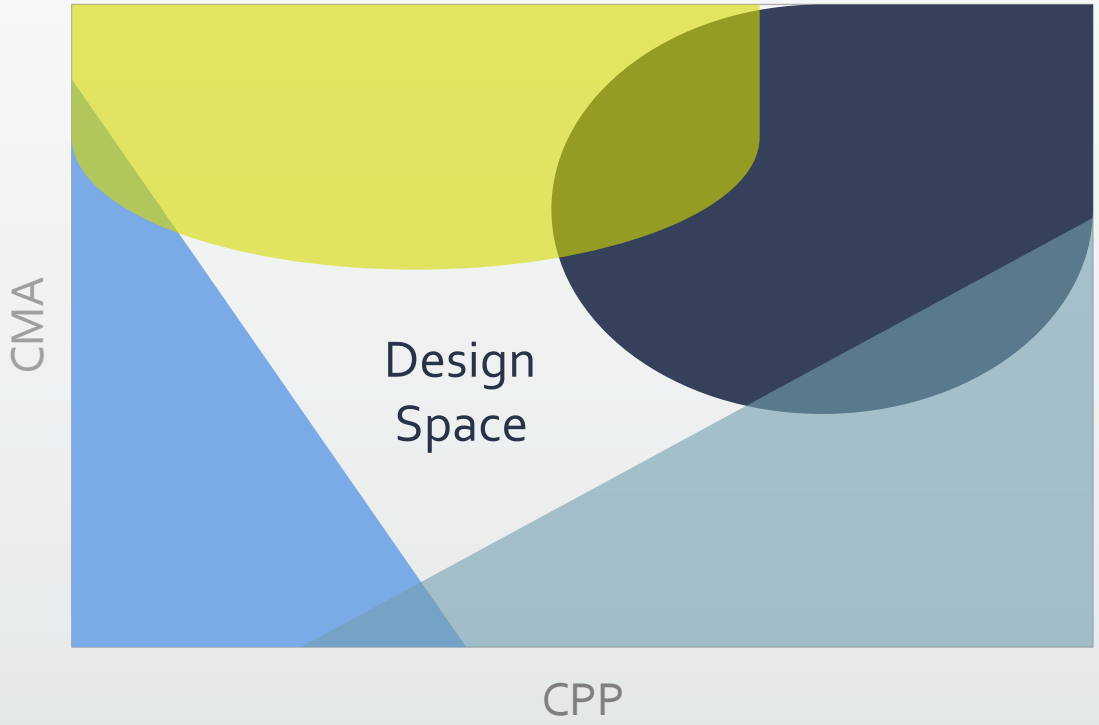
CPP
Critical Process Parameters

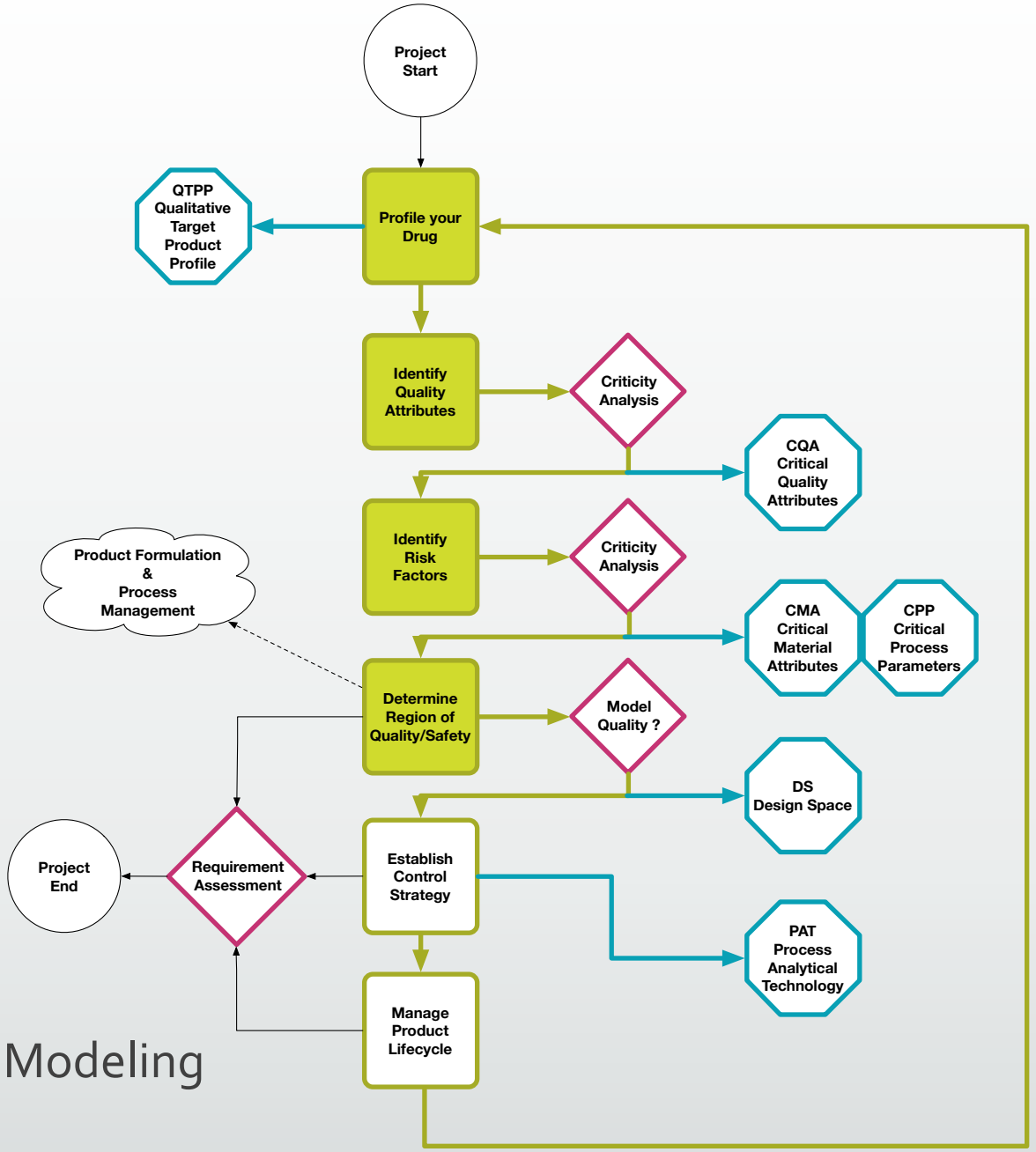
**How ?** Design of Experiments for Factor Screening



# QbD-4: Design Space ?

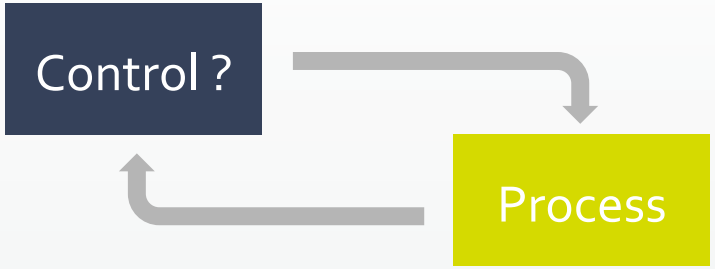
CQA = f(CMA,CPP)

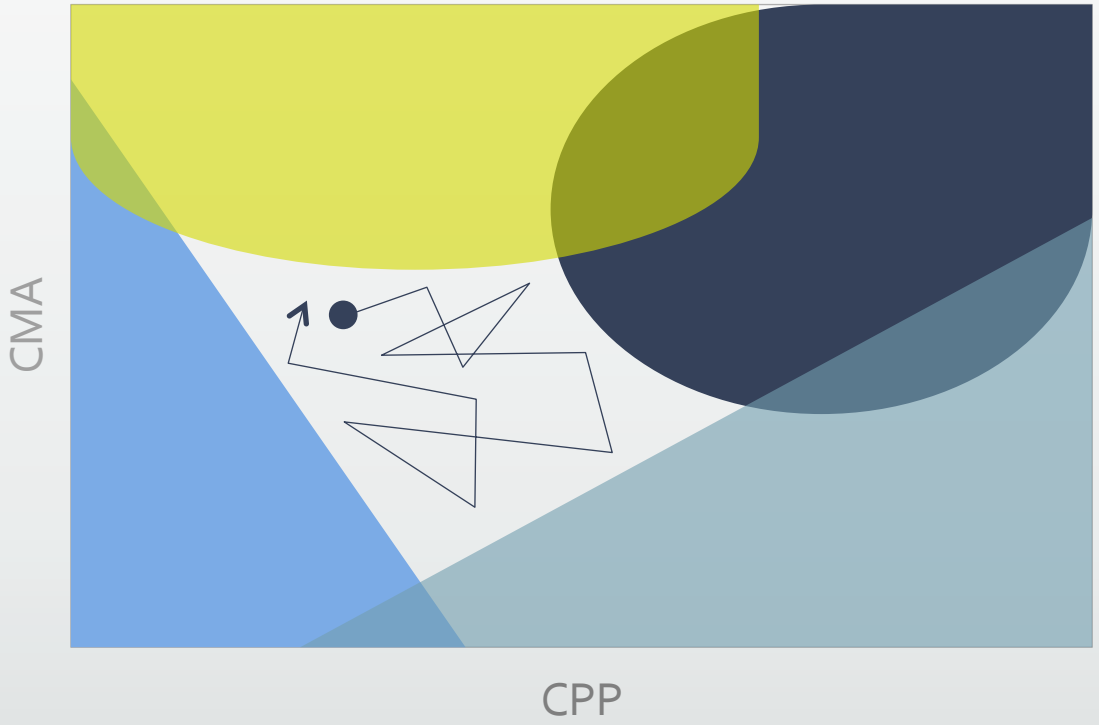


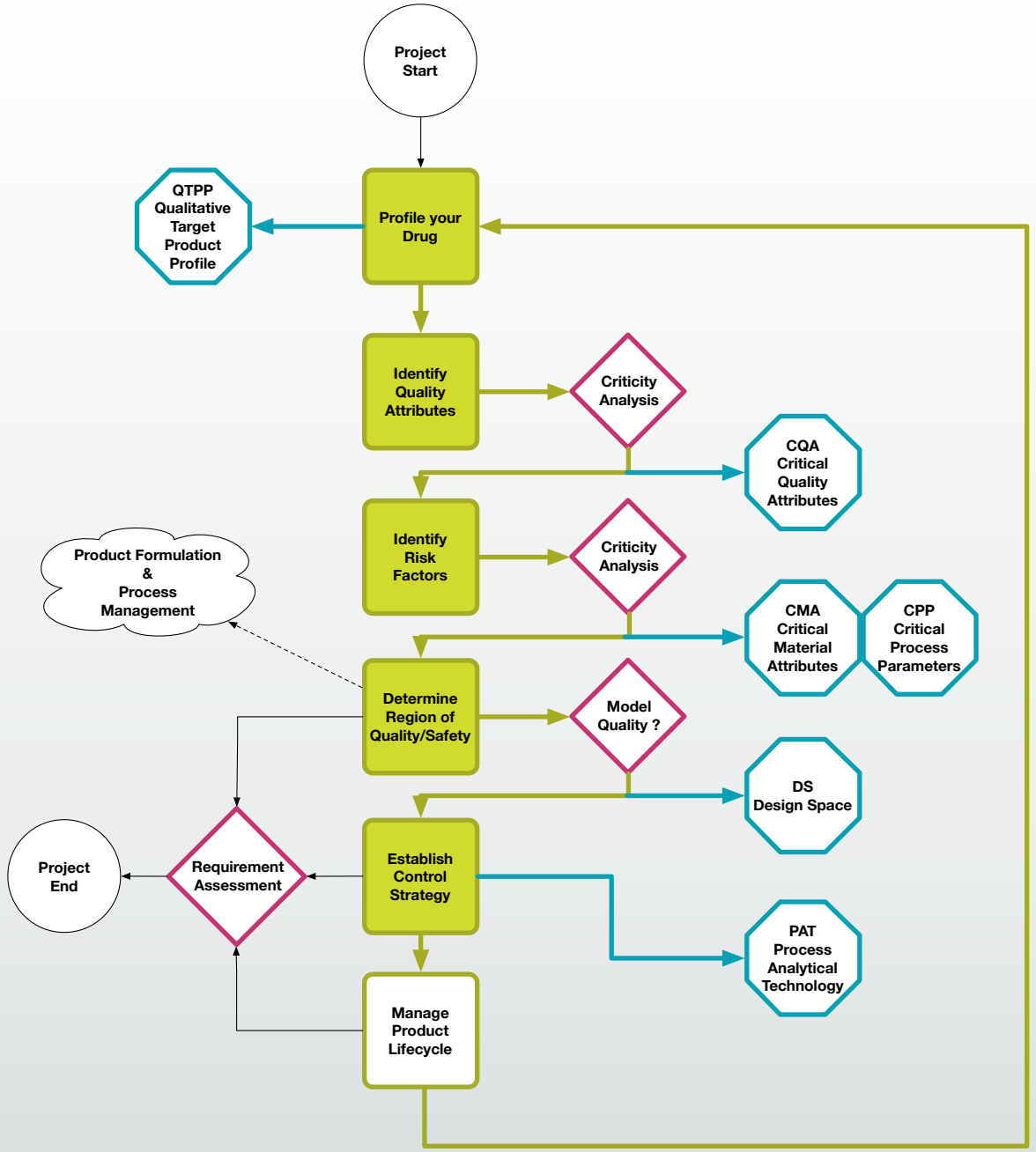




**How ?** Design of Experiments for Response Surface Modeling

# QbD-5: Control Strategy ?



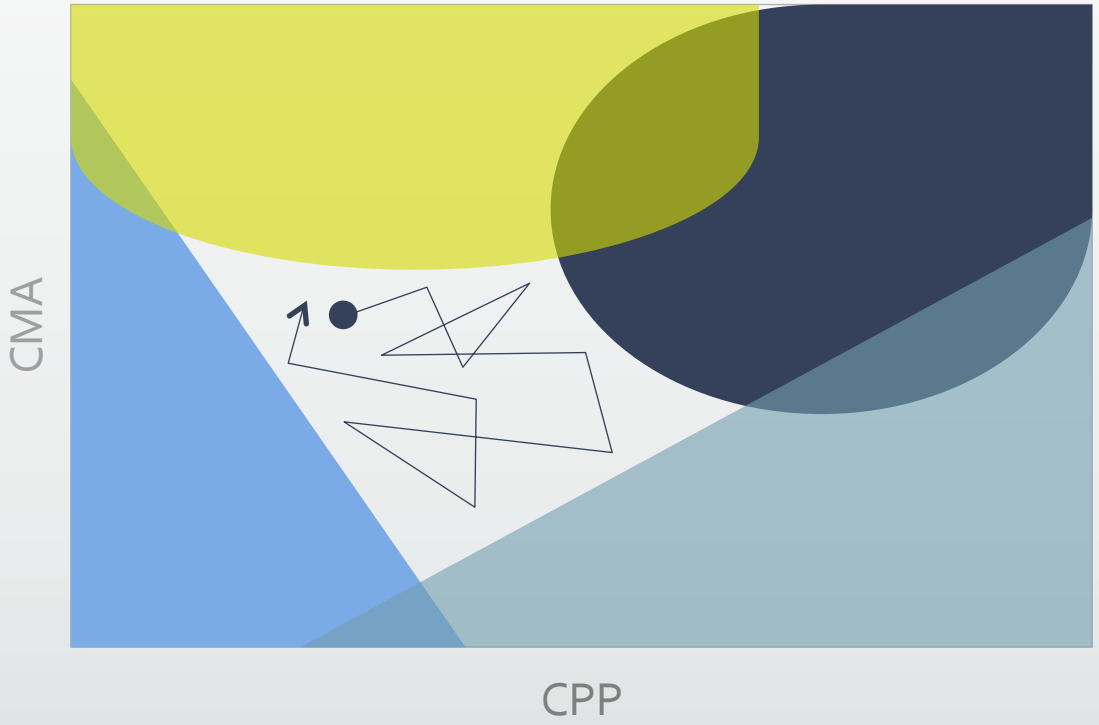



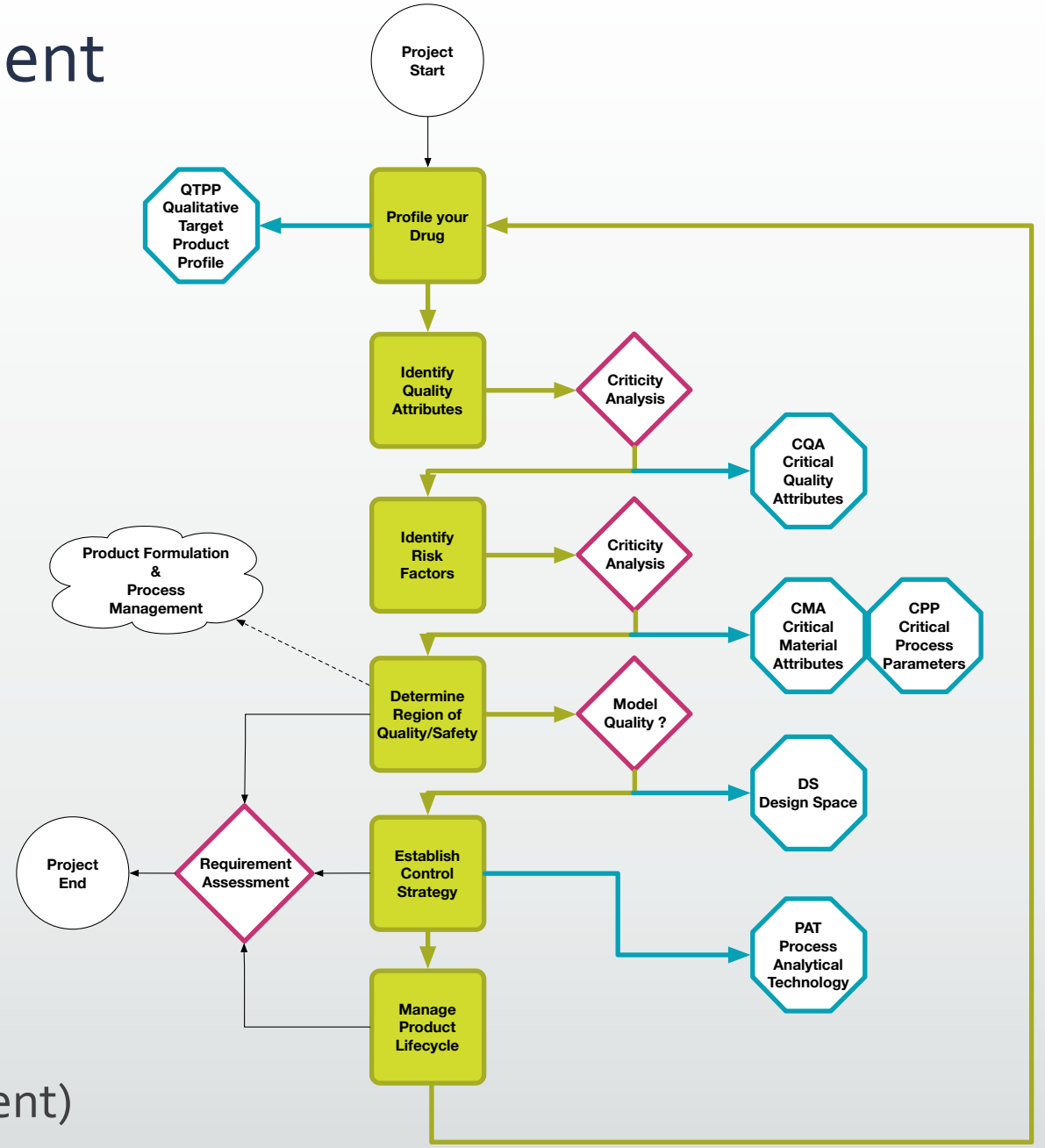




**How ?** Statistical Process Control

# QbD-6: Product LifeCycle Management



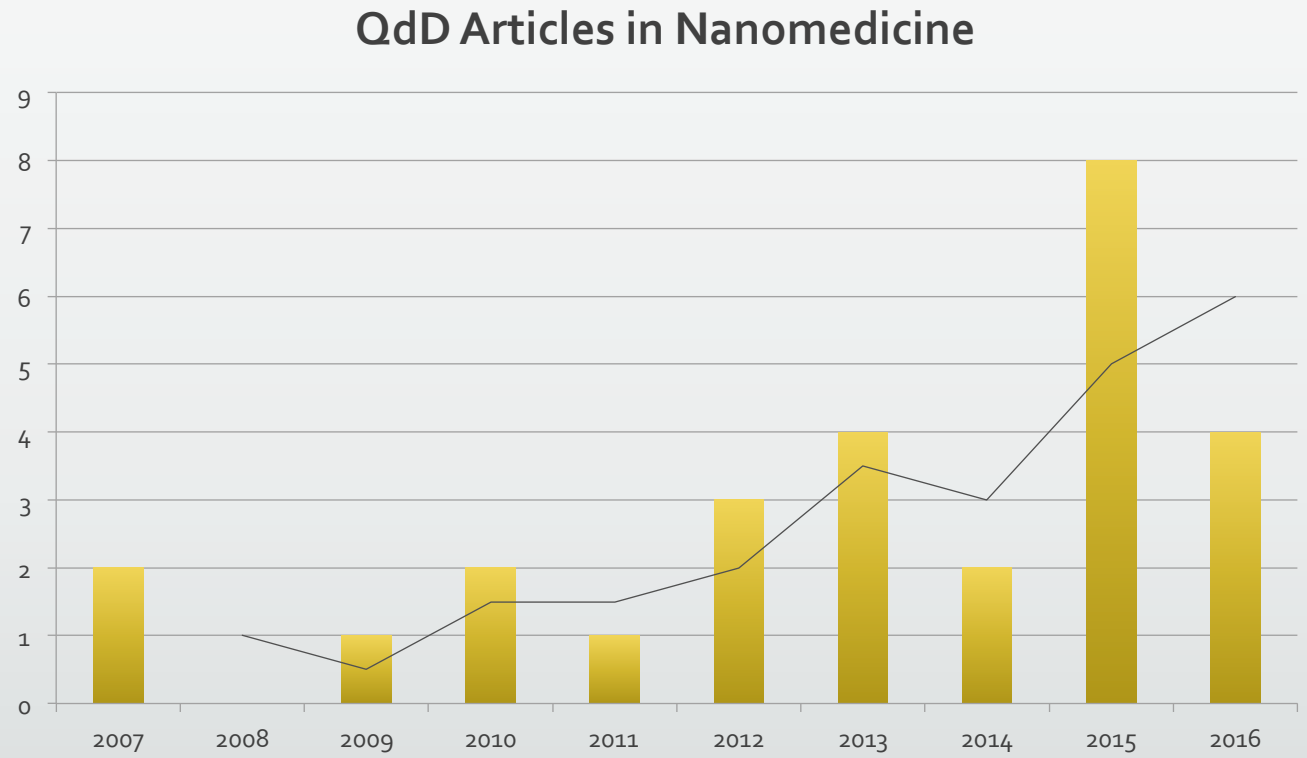




**How ?** PLM Methods (Product LifeCycle Management)

# 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



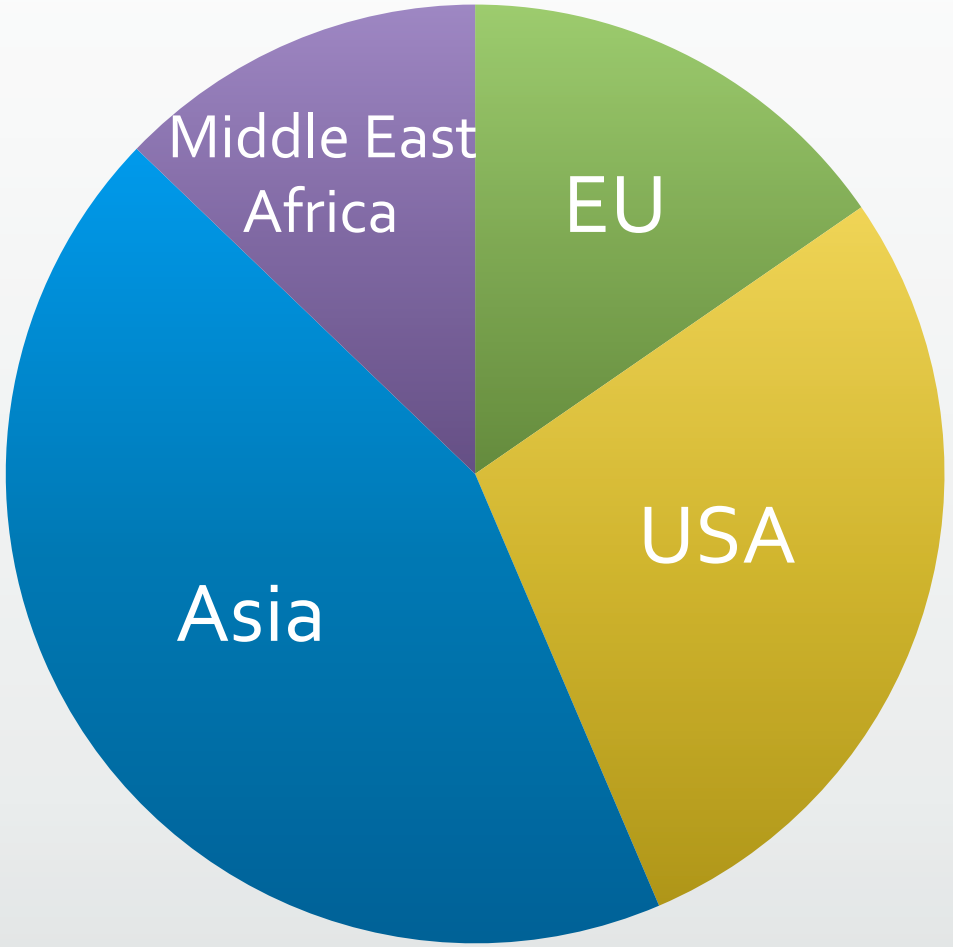

T. Bastogne, "Quality-by-design of nano-pharmaceuticals - A state of the art," Nanomedicine: Nanotechnology, Biology, and Medicine. June 2017.

Co-funded by the Horizon 2020
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**

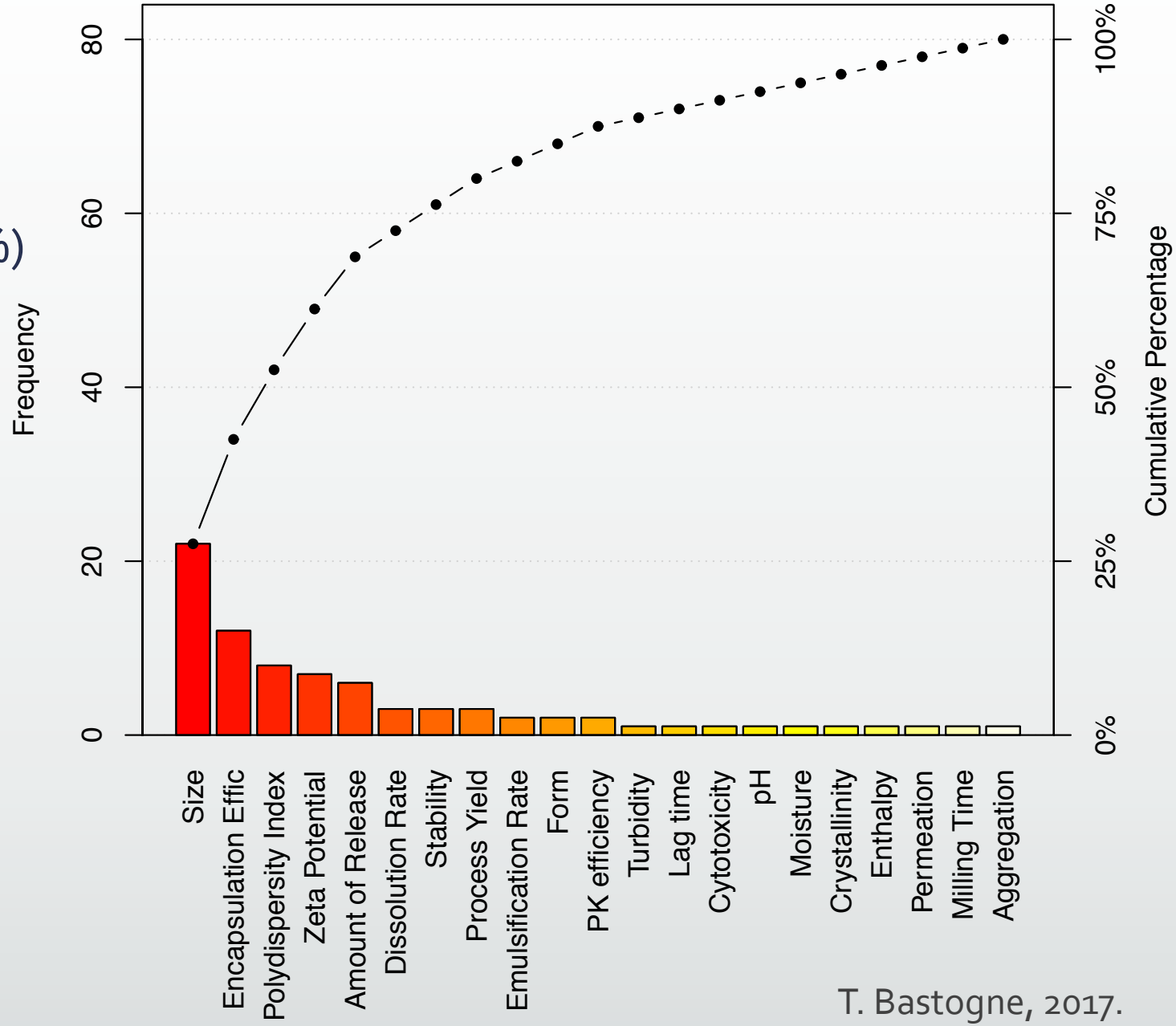
| QTPP elements | Target | Justification |
|---|---|---|
| Dosage form | Hydrogel | Pharmaceutical equivalence requirement: same dosage form |
| Route of administration | Injection | Pharmaceutical equivalence requirement: same route of administration |
| Dosage strength | % of drug substance (% w/w) | 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

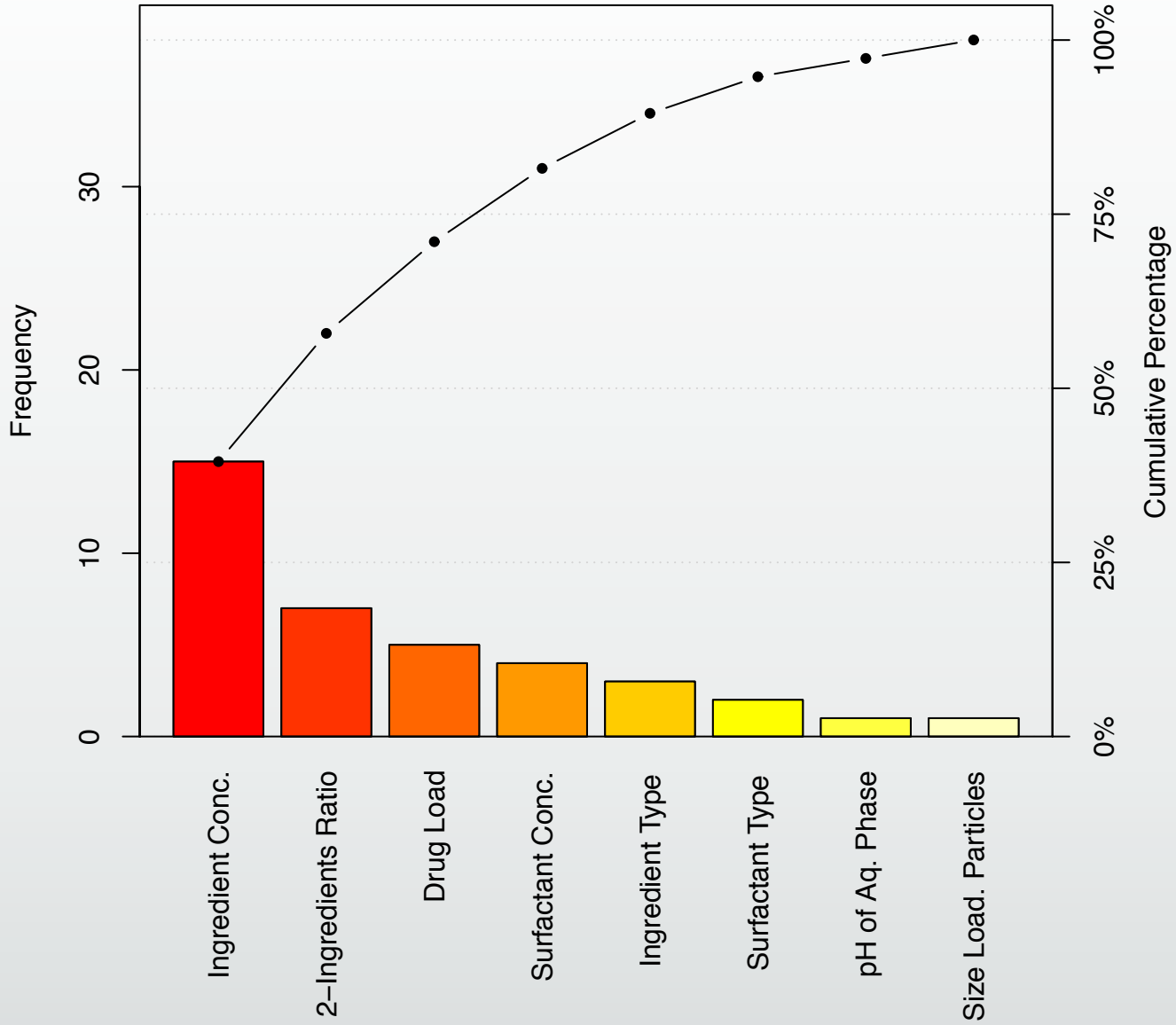



T. Bastogne, 2017.

# 3) CMA Specification

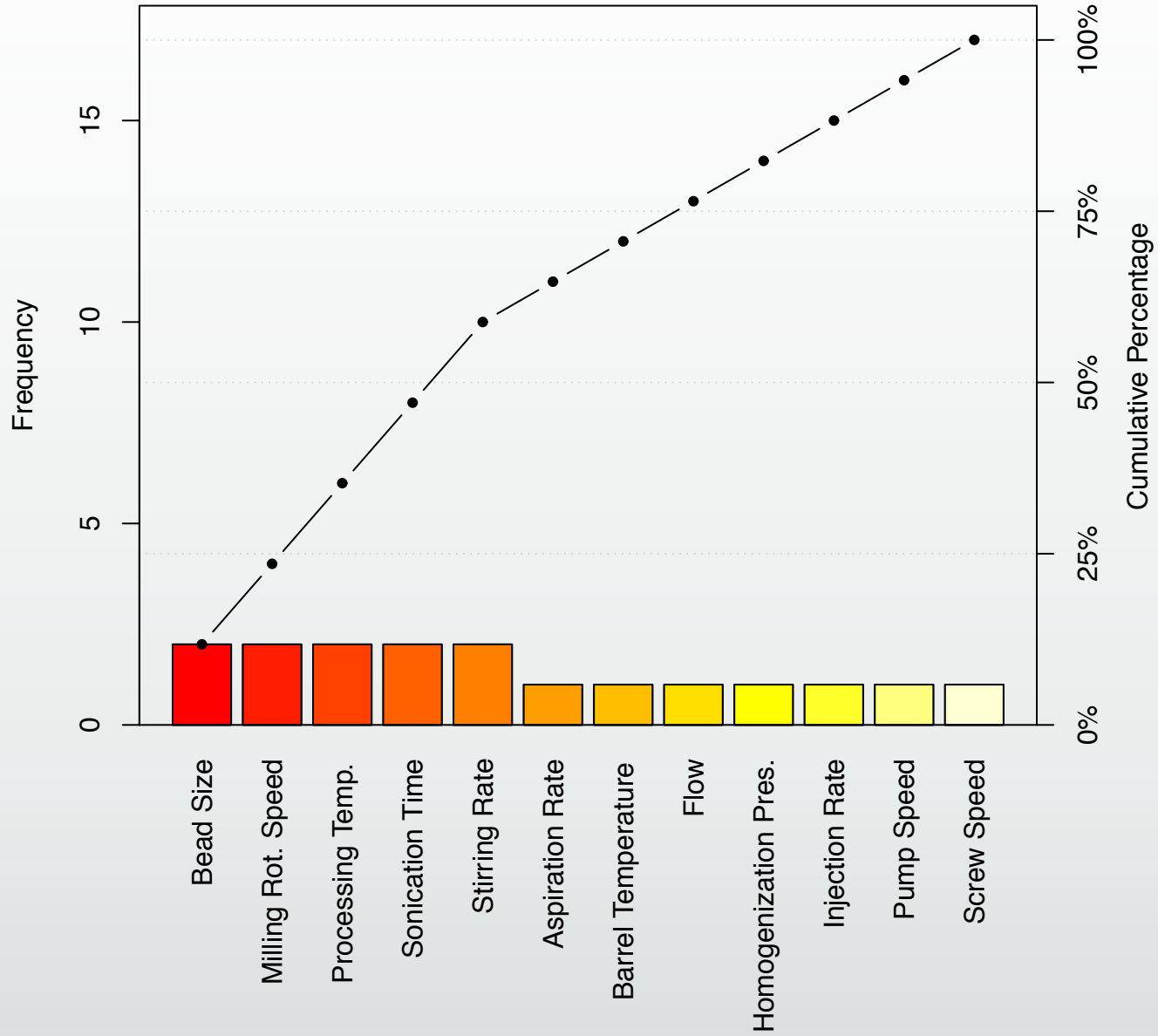
6 Criticial Material Attributes > 90%

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

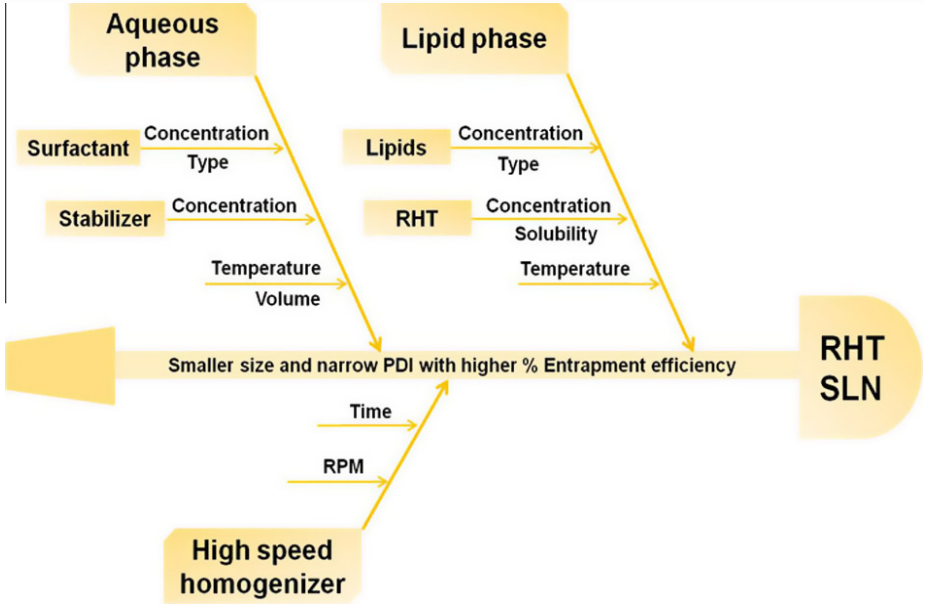



**Fig. 1.** Ishikawa diagram illustrating CPP affecting on CQA of RHT SLN.

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.

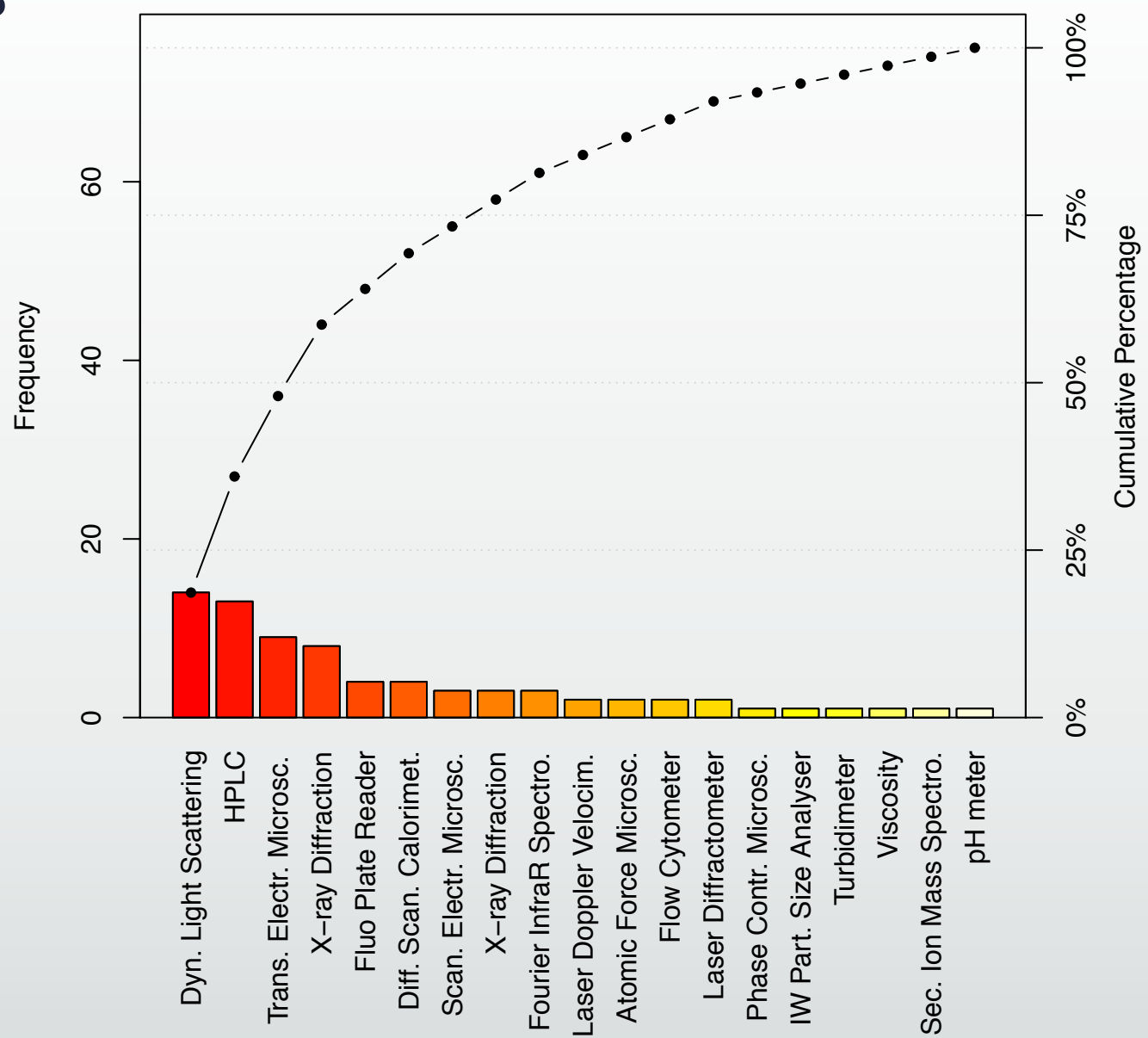
Criticity = Severity x Frequency

N.K. Garg et al., 2017

# Measurement Technologies

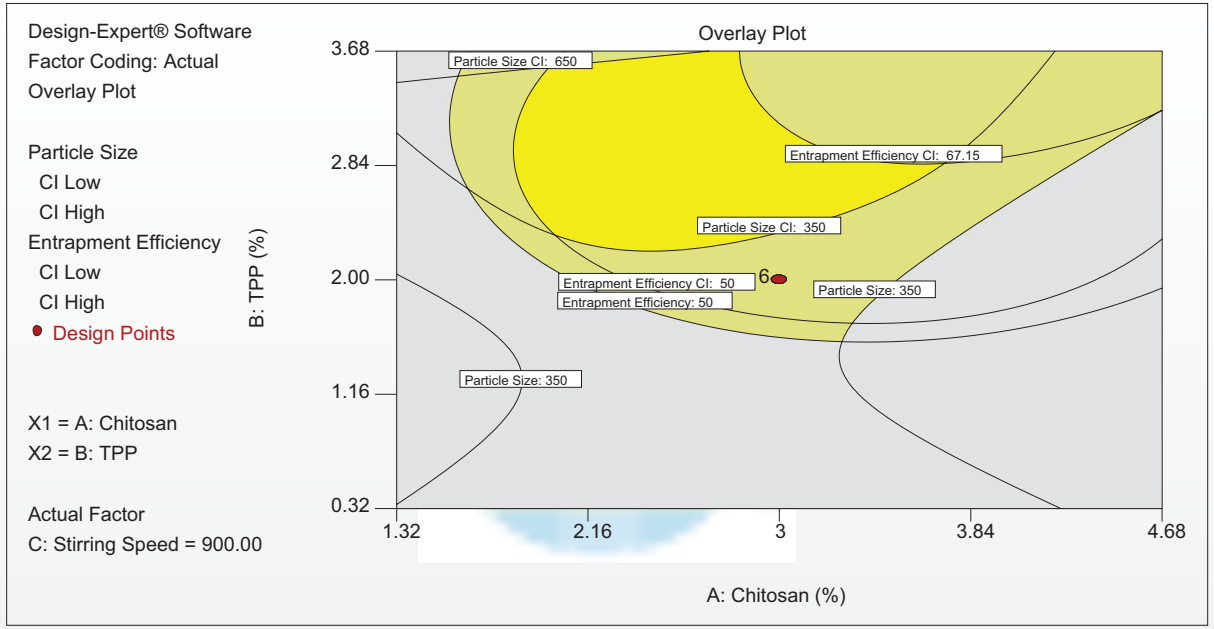
4 mian measurement techno. > 50%

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



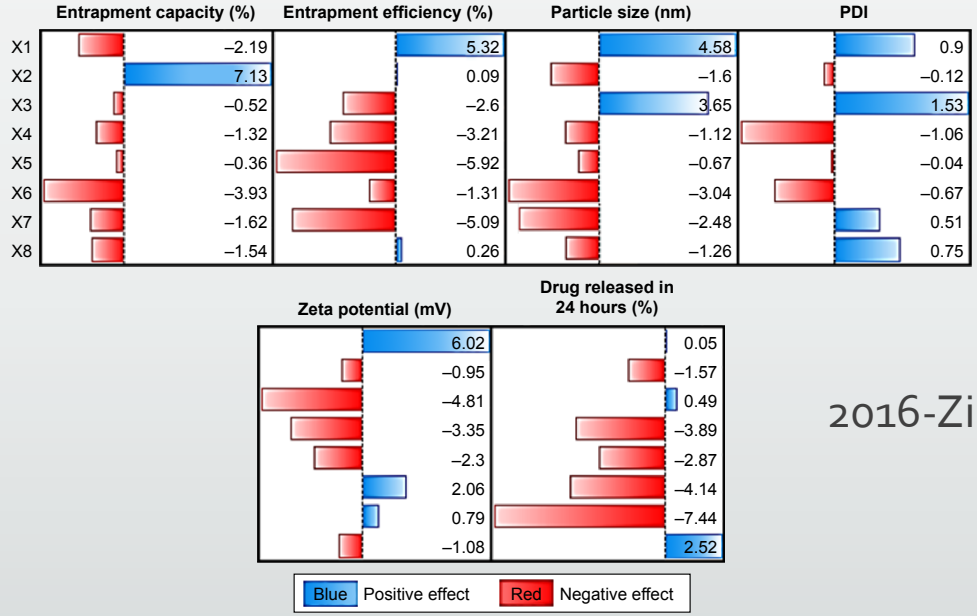
# Design of Experiments

- 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

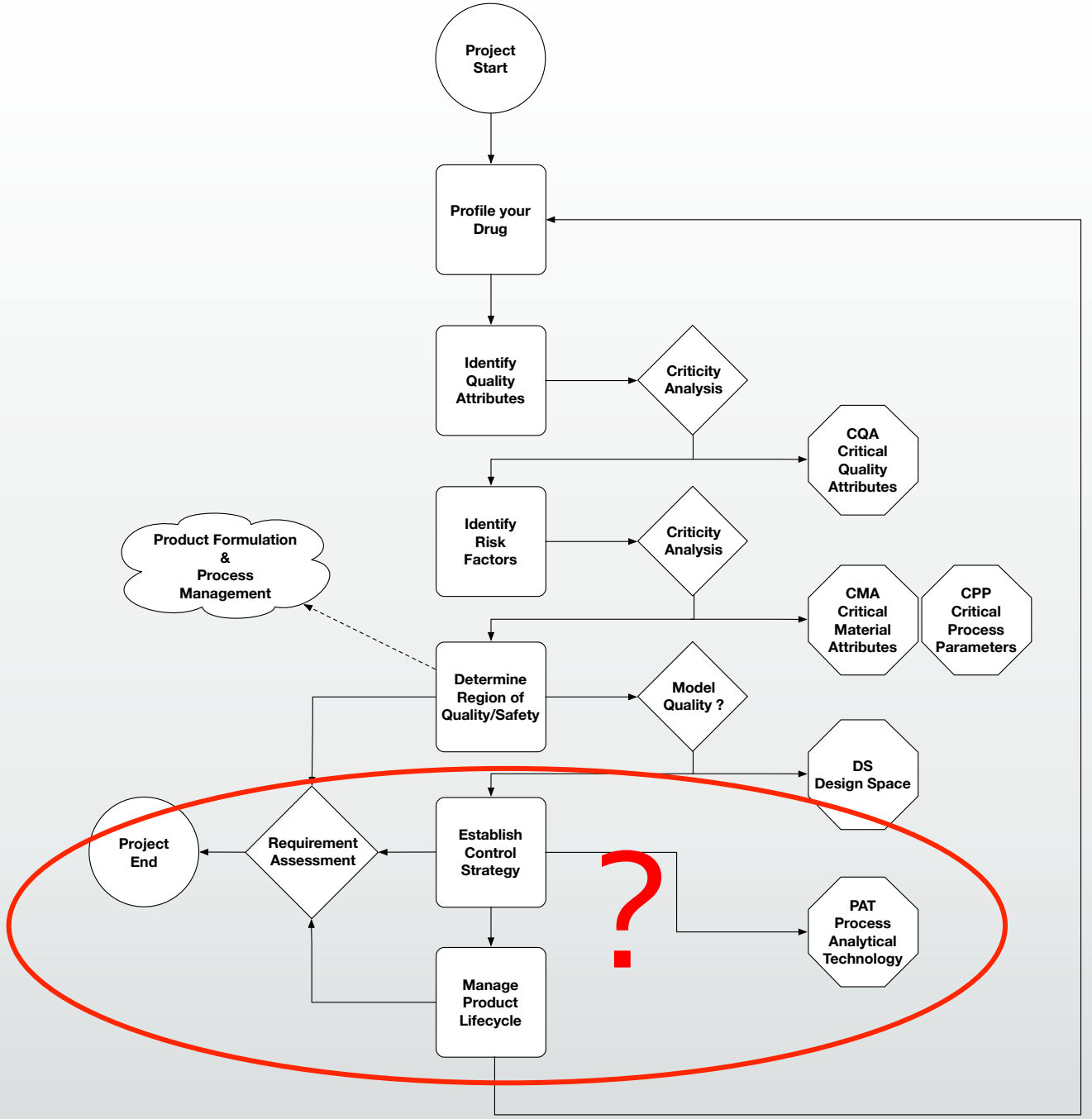
2015-Shirsat




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.

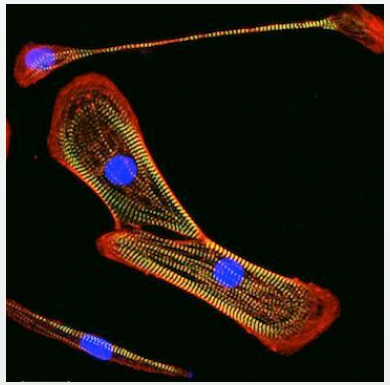
# Towards a new Cardio/Neuro-Toxicity Testing Model for Nano-Products

- **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).



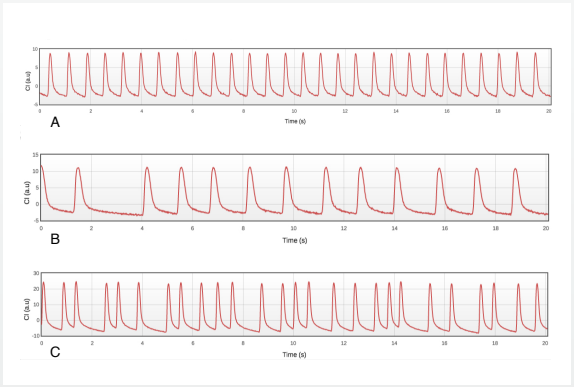
Multi-Electrode Arrays
Impedance-based Assays
Patch Clamp

+

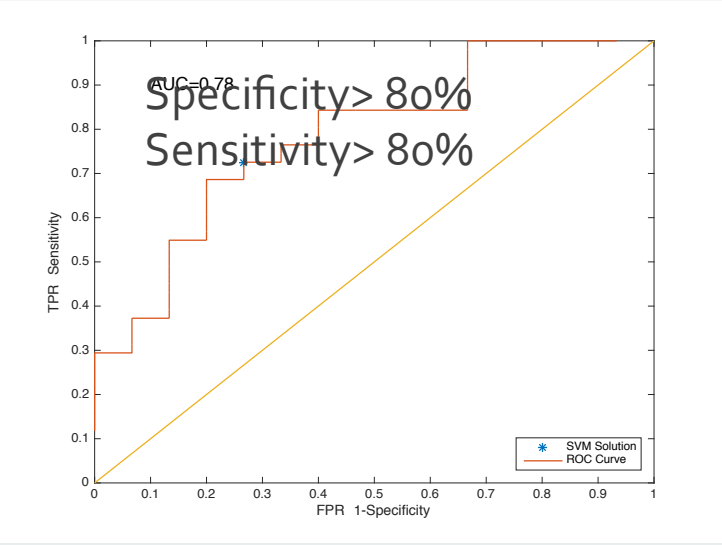


iPSC
human-iPSC-Derived
Cardiomyocites

+




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 ?