Quality by Design (QbD)

.

MPH 203 T & BP606

By

Dr. Abhishek Pandey
Assistant Professor

School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior

Contents

- What is Quality by Design (QbD)?
- What are tools to implement QbD?
- What are the key components of QbD?
- Closing remarks

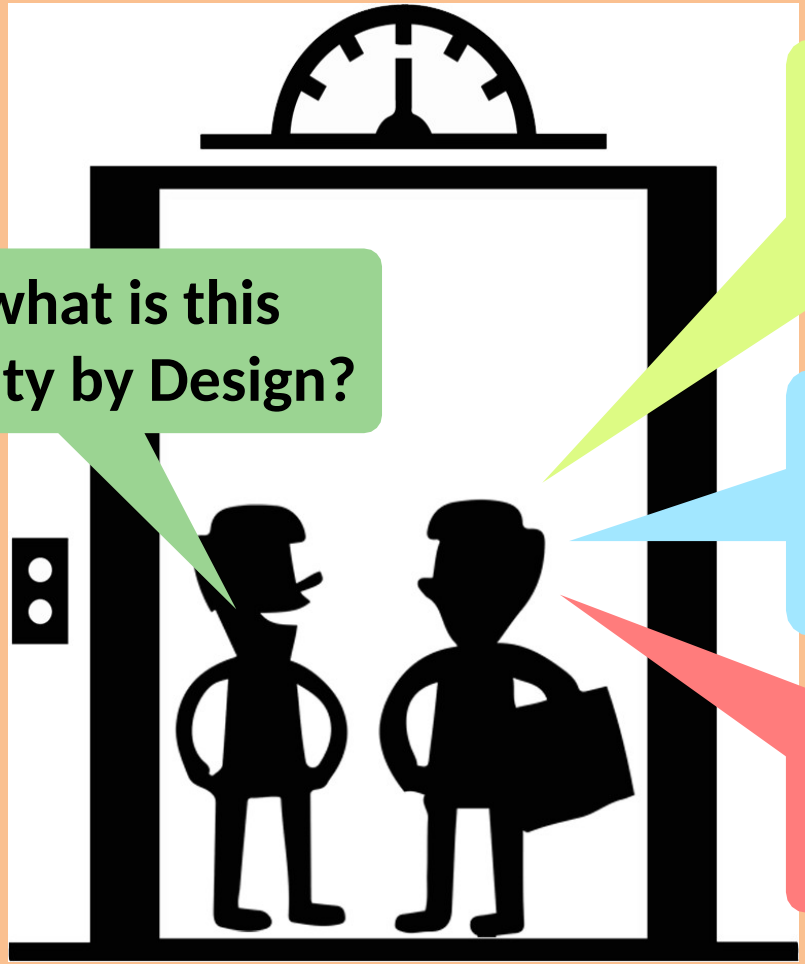
What is Quality by Design (QbD)?

Quality by Design (QbD)

is a concept first outlined by well-known quality expert Joseph M. Juran.

"Quality can be planned and most quality crises and problems relate to the way in which quality was planned in the first place."

Juran on Quality by Design (1992)



So…what is this Quality by Design?

Means

Designing and developing formulations and manufacturing processes to ensure a predefined quality.

Requires

Understanding how formulation and manufacturing process variables influence product quality.

Ensures

Product quality with effective control strategy.

Pharmaceutical Quality

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.

ICH Q6A, 2000

Pharmaceutical Quality = *f* (drug substance, excipients, process manufacturing …)

What are the consequences of Quality Failure?

- Lack of therapeutic effect leading to prolonged illness or even death;
- Toxic and adverse reactions;
- Waste of financial resources.

What are tools to implement QbD?

ICH Q9 Quality Risk Management

ICH Q8

Pharmaceutical Development:

- Drug substance development;
- Formulation development;
- Manufacture of investigational products;
- Manufacturing process development and scale-up;

Analytical method development.

ICH Q10

Pharmaceutical Quality System

Technology Transfer:

- New product transfers during development through manufacturing;
- Transfers within or between manufacturing and testing sites for marketed products.

Commercial Manufacturing:

- Acquisition and control of materials;
- Provision of facilities, utilities, and equipment;
- Production (including packaging and labelling);
- Quality control and assurance;
- Release.

Storage:

- Distribution (excluding wholesaler activities).

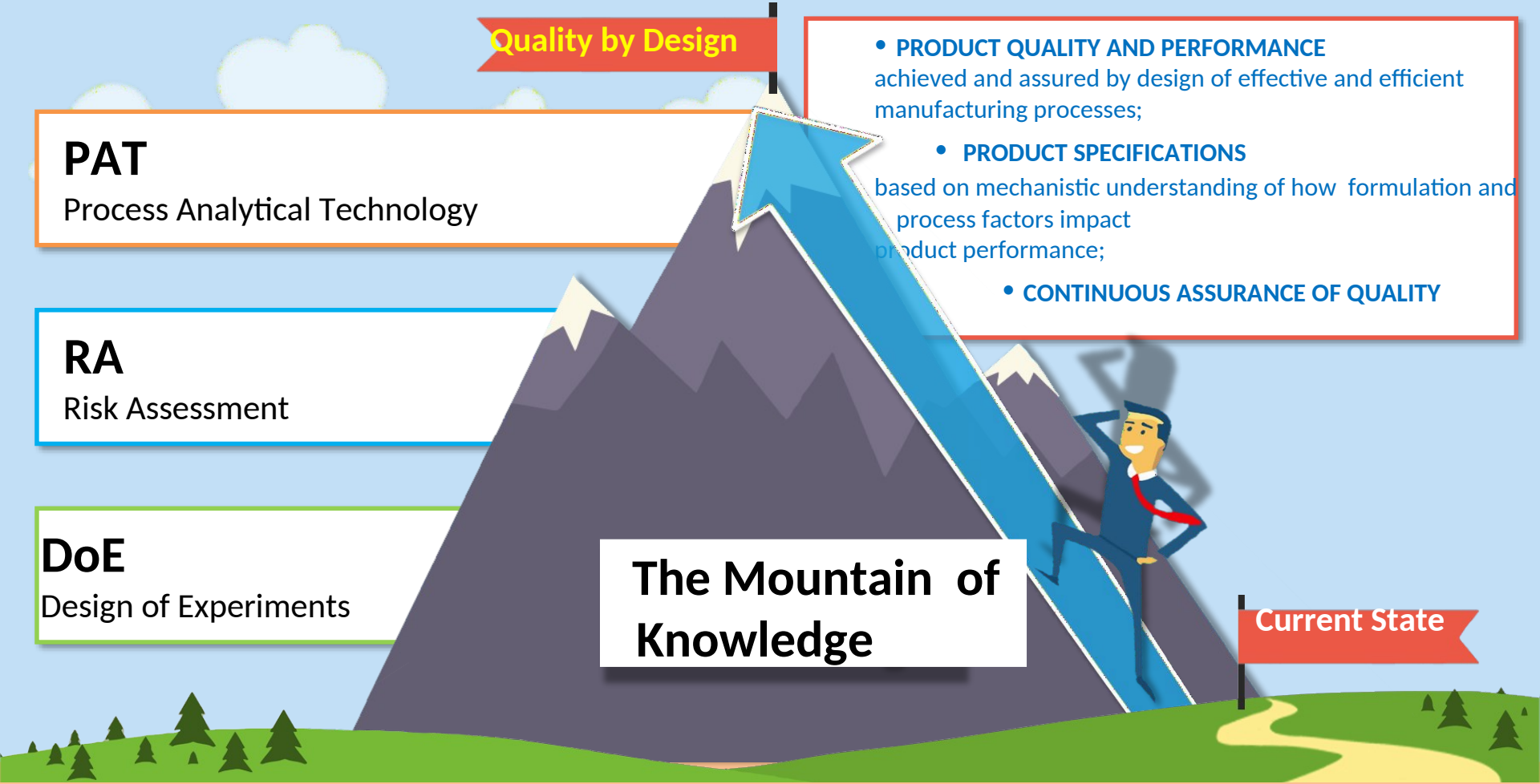
Product Discontinuation:

- Retention of documentation;
- Sample retention;
- Continued product assessment and reporting;

PAT
Process Analytical Technology

RA
Risk Assessment

DoE
Design of Experiments



- **PRODUCT QUALITY AND PERFORMANCE**
achieved and assured by design of effective and efficient manufacturing processes;
- **PRODUCT SPECIFICATIONS**
based on mechanistic understanding of how formulation and process factors impact product performance;
- **CONTINUOUS ASSURANCE OF QUALITY**

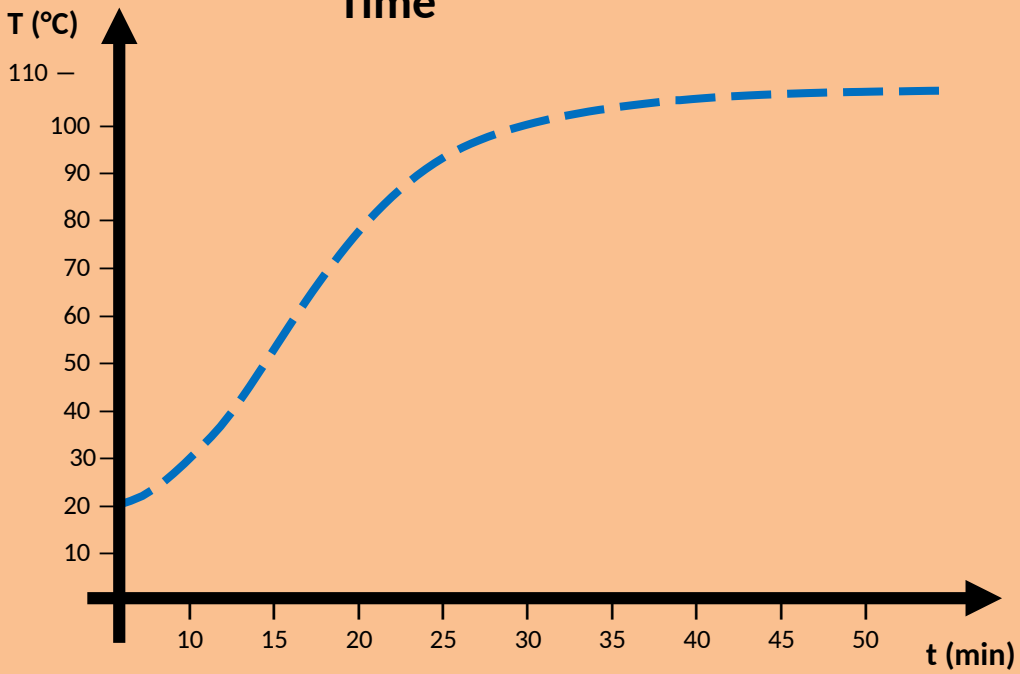
The properties of products and processes are affected by many factors:

Input factors **Process** **Output responses**

One factor at a time

This approach is based on varying one independent factor while keeping other factors constant.

Temperature vs. Time



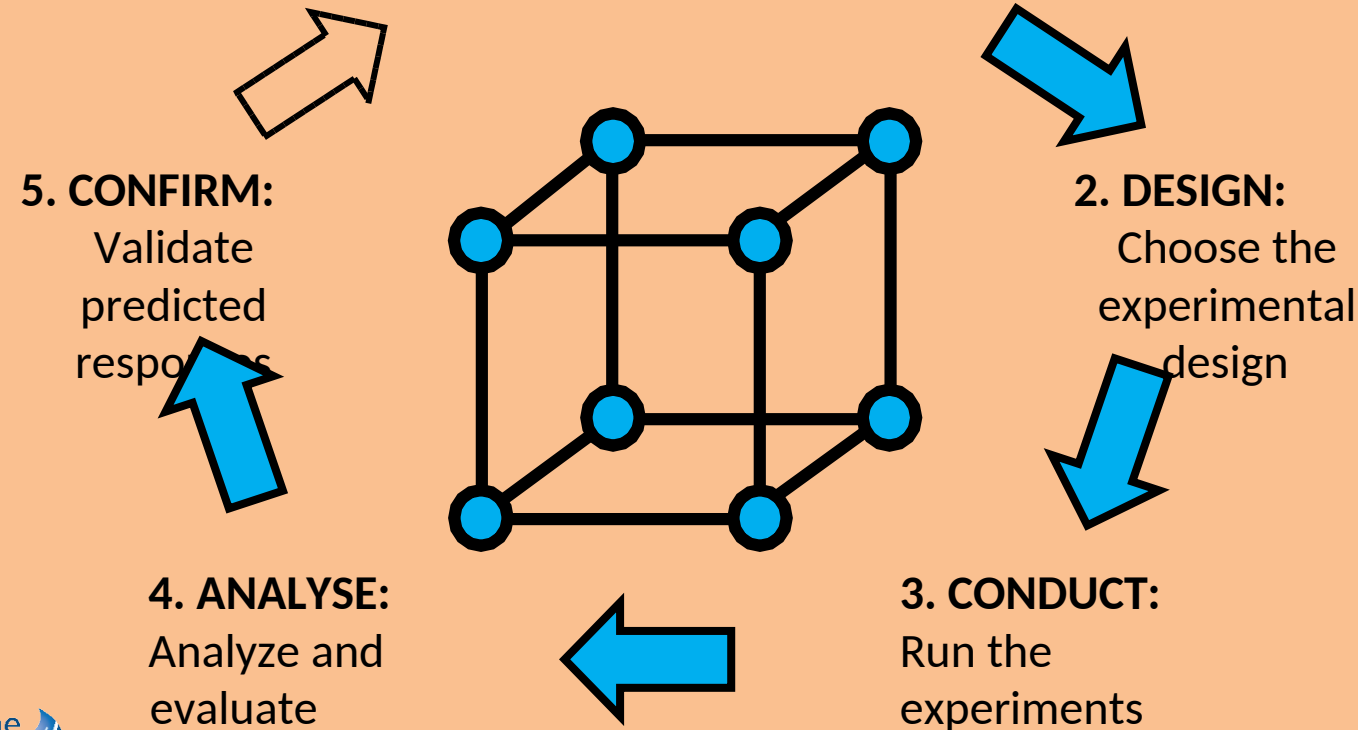
Disadvantages:

- One factor at a time experimentation frequently leads to sub-optimal solutions;
- Assumes the effect of one factor is the same at each level of other factors;
- This approach intrinsically cannot detect interactions between factors.

Design of Experiments (DoE)

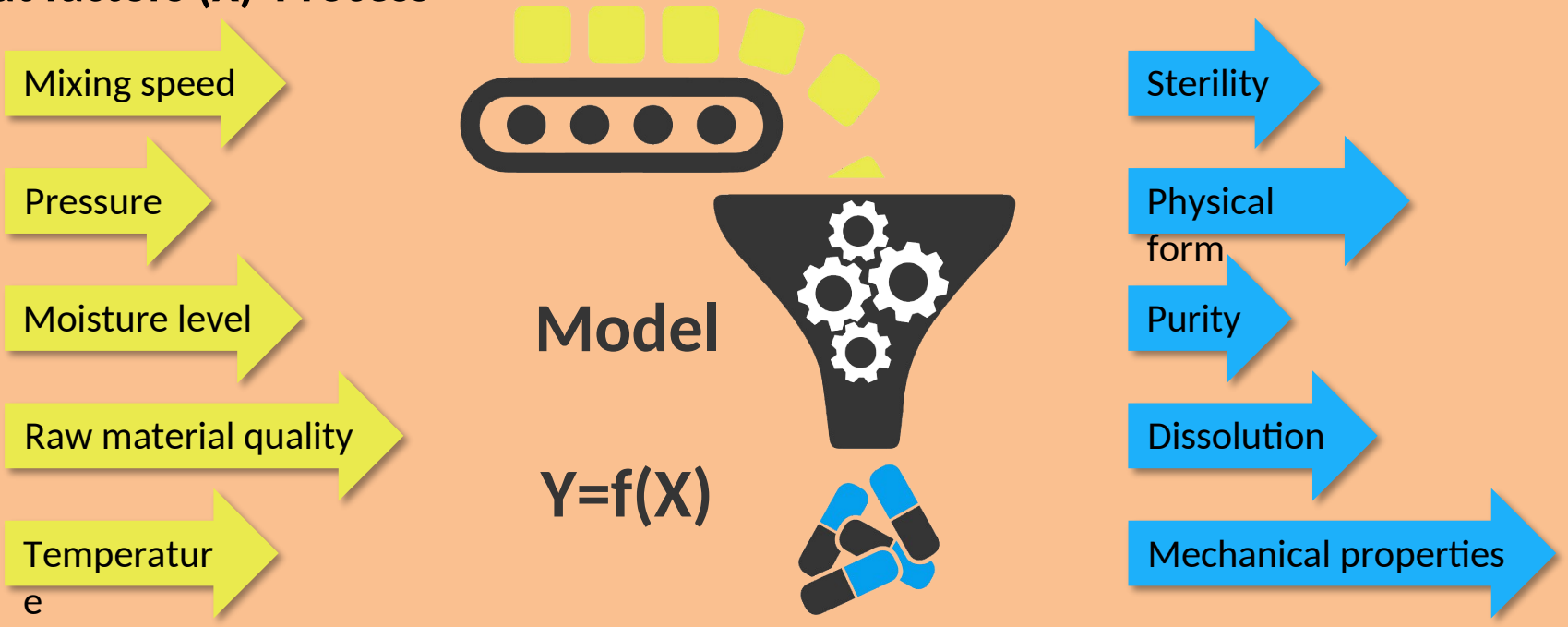
each single input variable and multi-variables interaction can be evaluated and their effects on each response variables can be identified.

1. PLAN: Identify factors and ranges to investigate



After DoE the process is not seen as a black box anymore.

Input factors (X) **Process** **Output responses (Y)**



Risk Assessment (RA)

consists of the identification of hazards and the evaluation of risks associated with exposure to those hazards.

As an aid to clearly defining the risks for RA, three fundamental questions are often helpful:

1. What might go wrong?

If anything can go wrong, it will.

2. What is the likelihood it will go wrong?

If anything just cannot go wrong, it will anyway.

3. What are the consequences?

It will be all your fault, and everyone will know it.

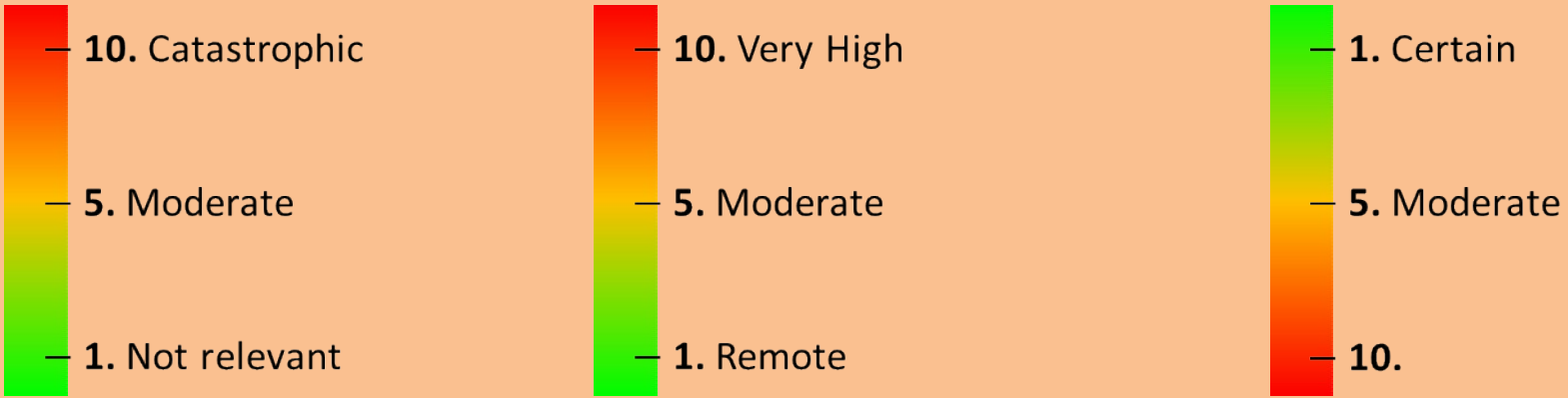
Murphy's Laws are not very useful for Risk Assessment!

Failure Mode, Effects, and Criticality Analysis (FMECA)

is a methodology to identify and analyse all potential failure modes and their effects. The output is a relative risk "score" for each failure mode, which is used to rank them on a relative risk basis.

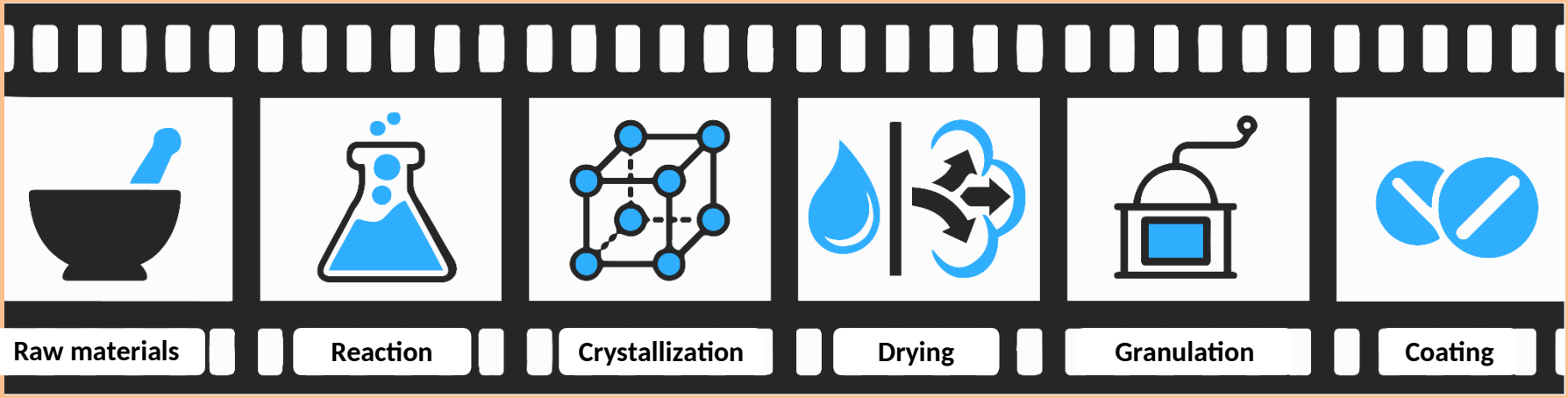
S x O x D = Risk Priority Number (RPN)

Severity of effect (S)	Occurrence probability (O)



Process Analytical Technology (PAT)

is a system for designing, analysing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw, in process materials and processes with the goal of ensuring final product quality.



Key components of QbD

Target Product Profile (TPP)

is patient and labelling centred concept, which includes:

Mechanism of action

The mechanism by which the product produces an effect on a living organism.

Clinical pharmacology

Pharmacokinetic information, distribution and pathways for transformation.

Indication for use

Target disease or manifestation of a disease and/or population.

Primary efficacy endpoints

The most important clinical outcome measure.

Secondary efficacy endpoints

Additional criteria that may be met during a clinical trial, but that are not required to obtain a successful positive clinical trial result.

Step 1 - Categorization of Drug Properties

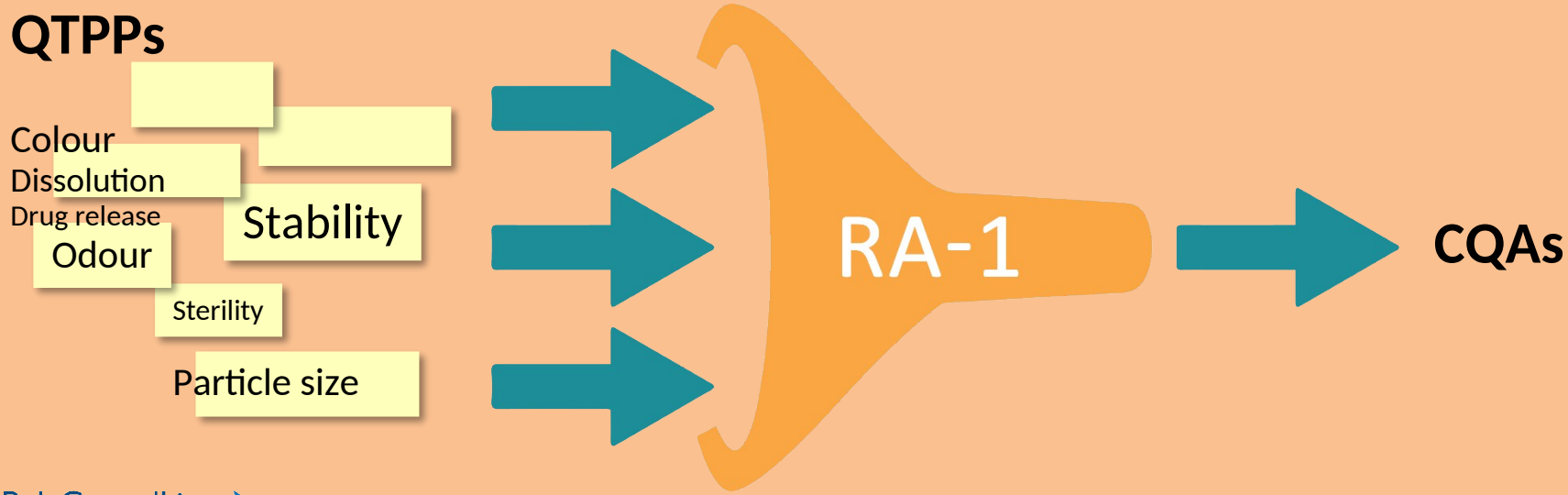
Quality Target Product Profile (QTPP)

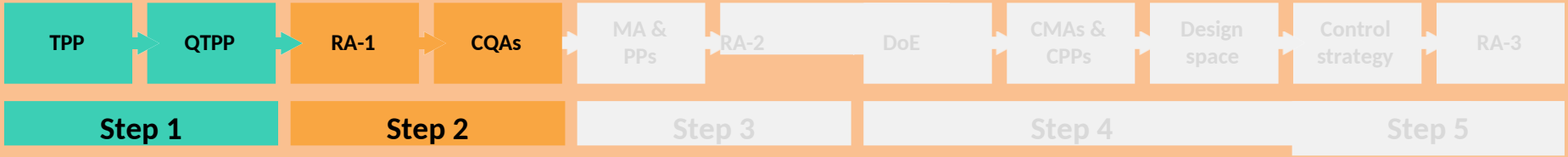
is a quantitative surrogate for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process, which includes quantitative targets for:

- **Indication and route of administration**
- **Dosage form and strength**
- **Container closure system**
- **Attributes affecting pharmacokinetic characteristics** (i.e. dissolution and aerodynamic performance)
- **Drug product quality criteria** (i.e. sterility, purity, stability and drug release)

Initial Risk Assessment (RA-1)

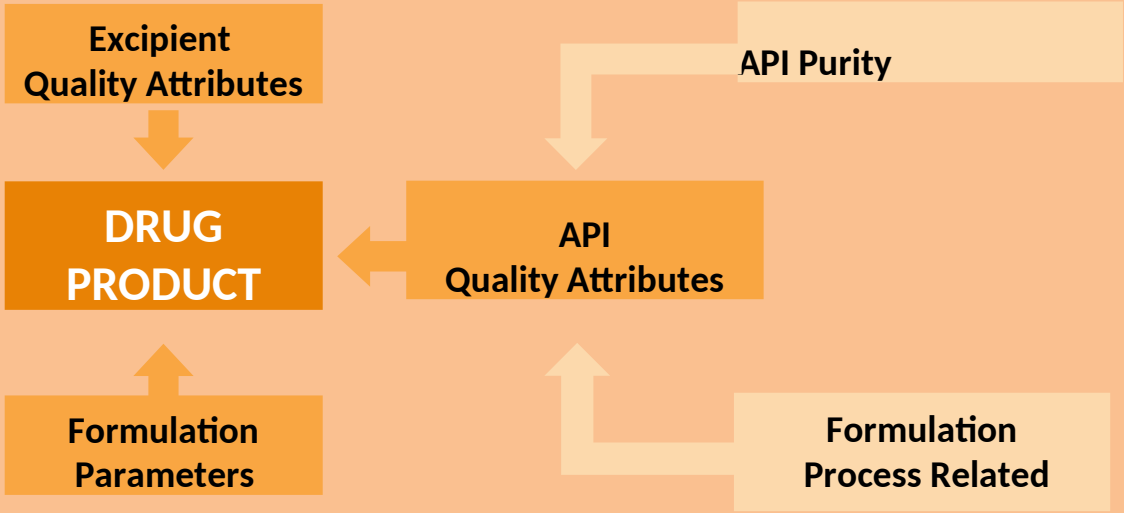
an initial risk assessment is carried out to shortlists the QTPPs that are critical for the patients.

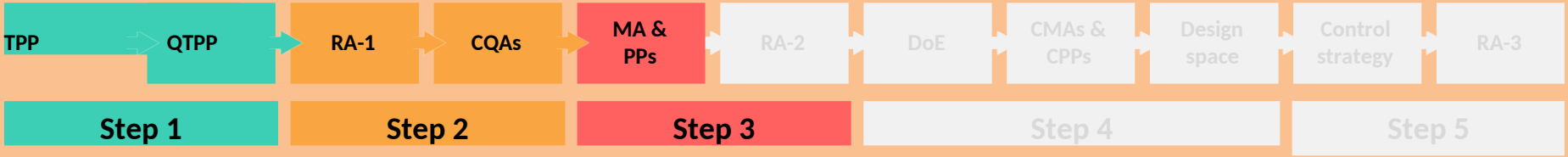




Critical Quality Attributes (CQAs)

are attributes that should be within an appropriate limit or distribution to ensure the desired quality.





Material Attribute (MA)

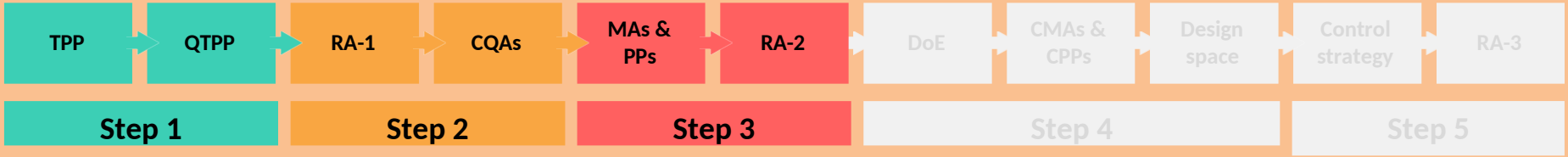
is any physical, chemical, biological or microbiological property of materials, such as:

Purity | Porosity | Moisture level | Specific volume | Sterility

Process Parameter (PP)

is any input operating parameter of a process, such as:

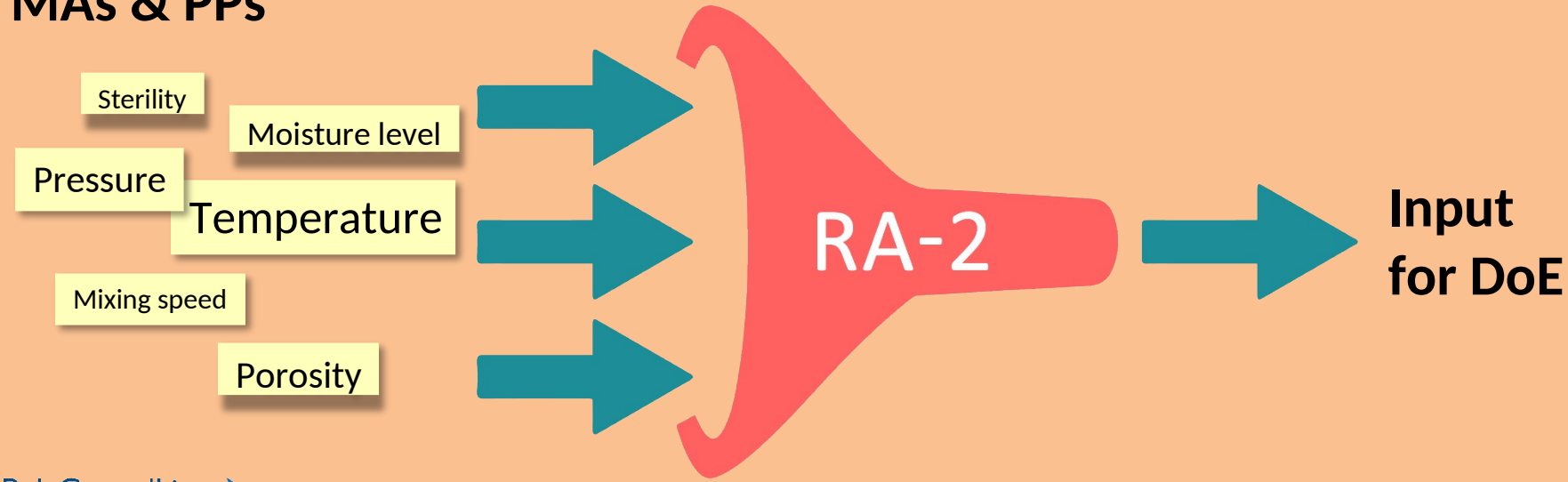
Mixing speed | Flow rate | Temperature | Pressure



Risk Assessment after development (RA-2)

a second risk assessment is performed to identify the important input variables for the DoE.

MAs & PPs

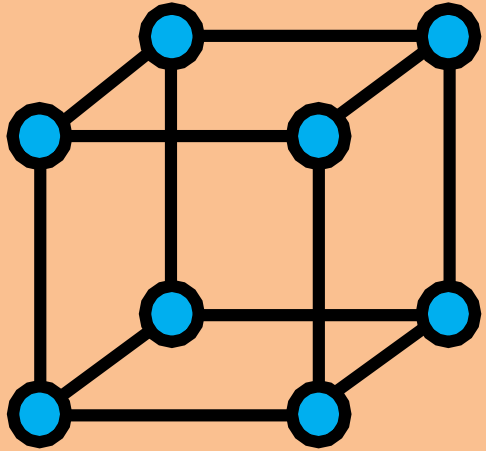


TPP → QTPP → RA-1 → CQAs → MA & PPs → RA-2 → DoE → CMAs & CPPs → Design space → Control strategy → RA-3

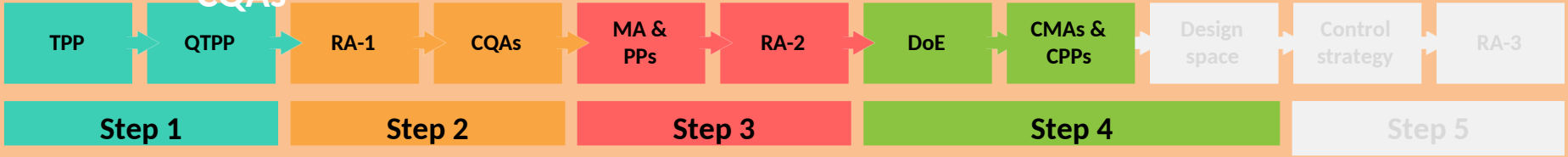
Step 1 | Step 2 | Step 3 | Step 4 | Step 5

Design of Experiments (DoE)

the output of the DoE is the set of variables that affect the CQAs significantly.

Input for DoE →  → **CMAs & CPPs**

Step 4 - Optimization of the Effects of the Input Variables on the CQAs



Critical Material Attributes (CMAs)

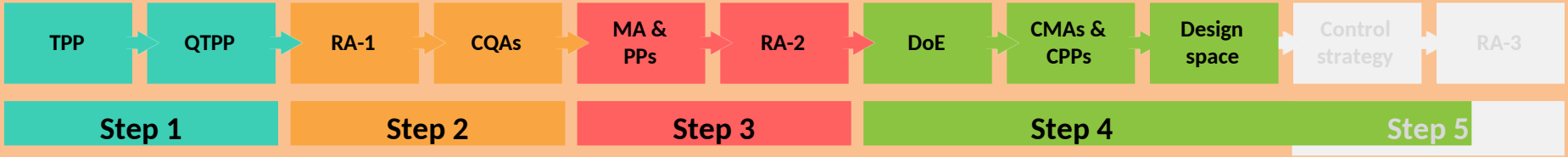
are MAs that need to be controlled to ensure the desired quality.

CMAs are independent of each other (i.e. Particle Size and Purity)

Critical Process Parameters (CPPs)

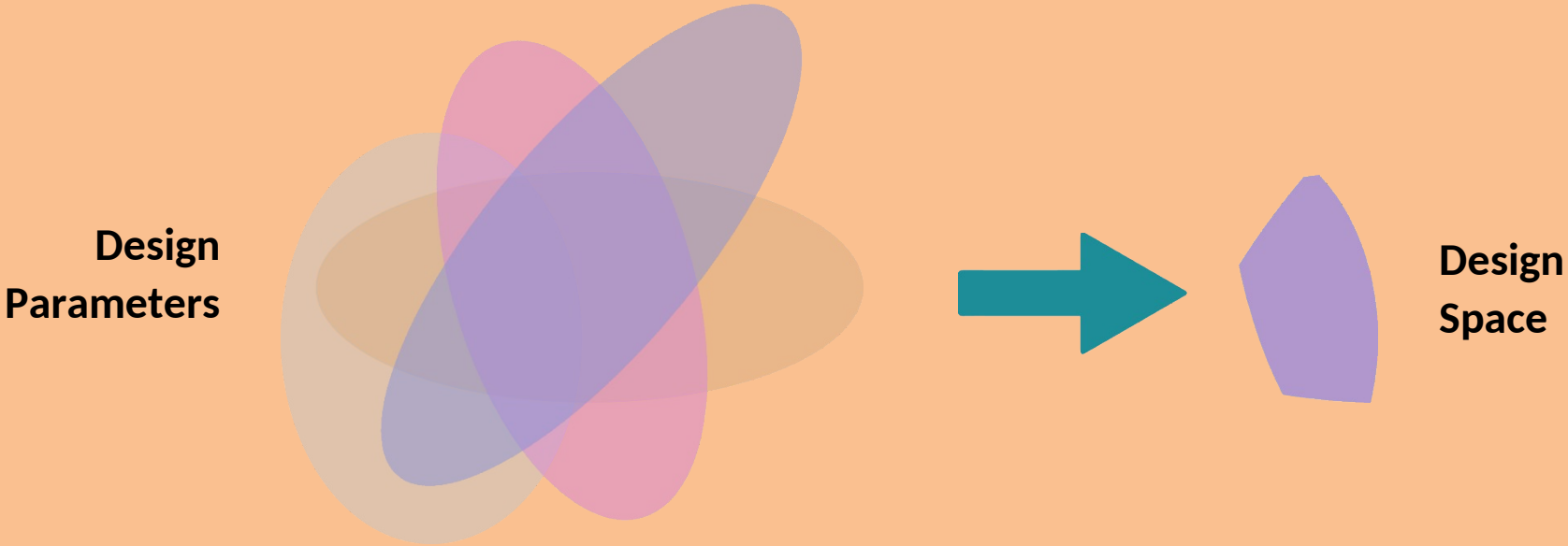
are PPs that can cause the product to fail to meet the desired quality.

Temperature | Cooling rate | Rotation speed | Agitation | Feed type and rate | pH

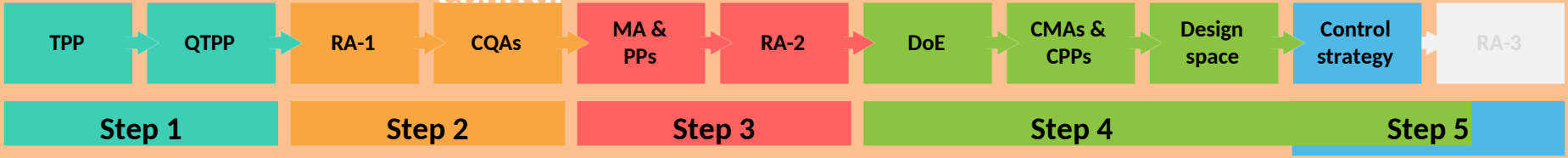


Design Space (ICH Q8)

is an established multidimensional combination and interaction of MAs and PPs demonstrated to provide assurance of quality.



Step 5 - Control Strategy and Risk Control

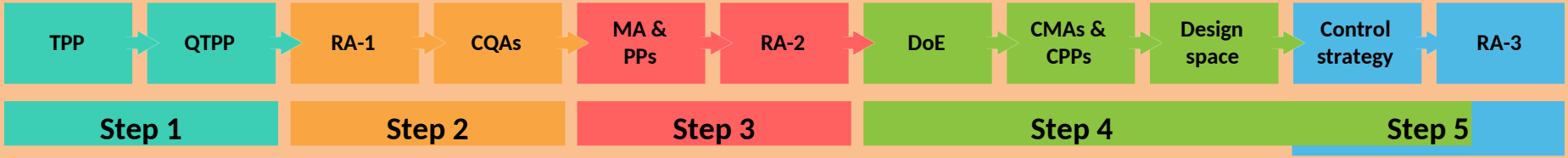


Control Strategy (ICH Q10)

is a planned set of controls derived from current product and process understanding that assures process performance and product quality. Elements of a control strategy can include:

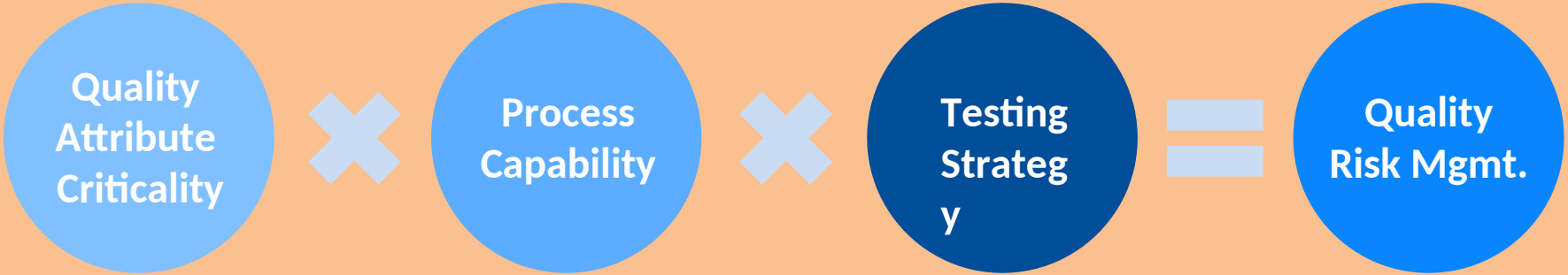
- Identification and qualification of raw materials
- Quantitative determination of active ingredients in finished products
- Quantitative discrimination of physiochemical parameters in finished products
- In-process control of physiochemical parameters

PAT

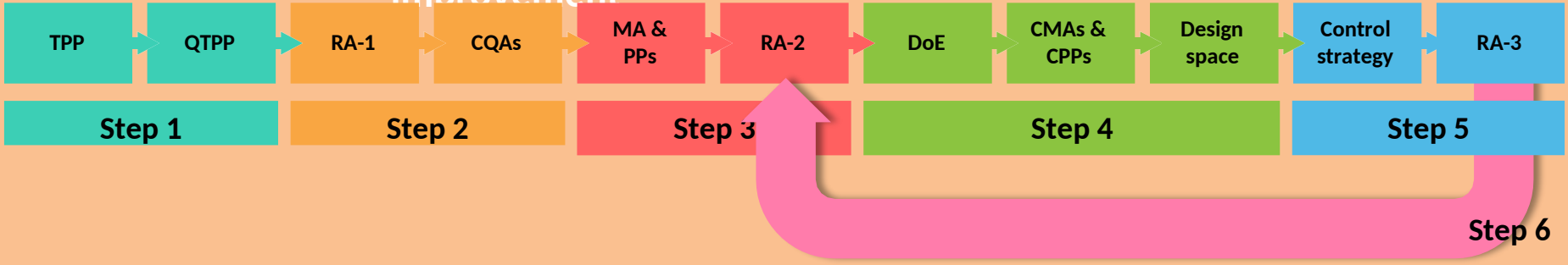


Risk Assessment after implementation of control strategy (RA-3)

risk to the CQAs is re-evaluated to determine whether it has been reduced after optimization with respect to the risk that existed during RA-2.



Step 6 - Feedback for continuous improvement



Feedback for continuous improvement

the pursuit of continuous improvement can be translated in the Japanese productivity philosophy known as Kaizen, which simply means “change for better”.

改善

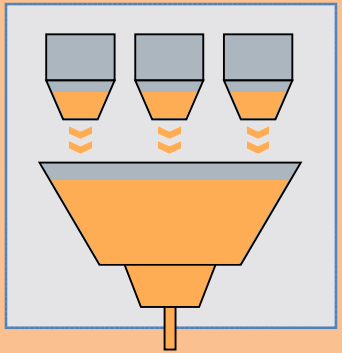
KAI • ZEN

Closing remarks

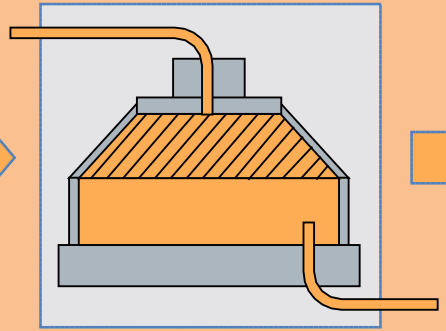
An example of QbD process

Granulation Drying

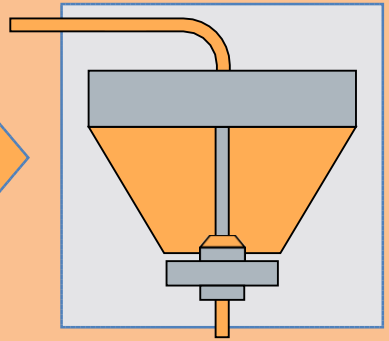
Dispensation



Identity
NIR, RAMAN

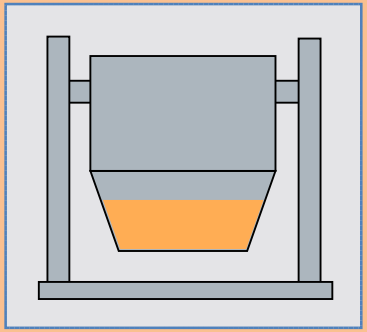


Particle size
FBRM



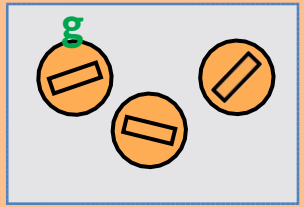
Rate of drying
NIR

Blending



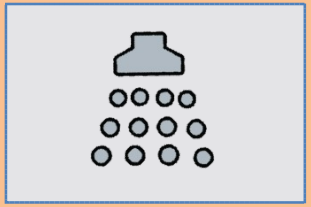
Blend homogeneity
NIR, RAMAN

Tabletin



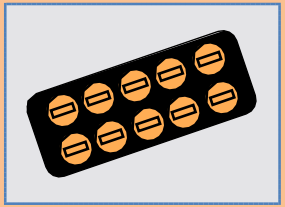
Content uniformity
NIR

Film coating



Coating quality
Digital imaging

Packaging



Blister quality
FEA & 3D Scanning

Unit operation

CQA

PAT

PolyCrystalLine
experts in crystal forms

www.polycrystalline.it

Why use Quality by Design?

- Provides a proactive approach to product development, potential to reduce queries and review time to quickly get to the root cause and resolution of any deviation;
- Allows for continuous improvements in products and manufacturing process;
- Allows for better understanding of how APIs and excipients affect manufacturing;
- Increase manufacturing efficiency, reduce costs and waste.

Thank you for the Attention