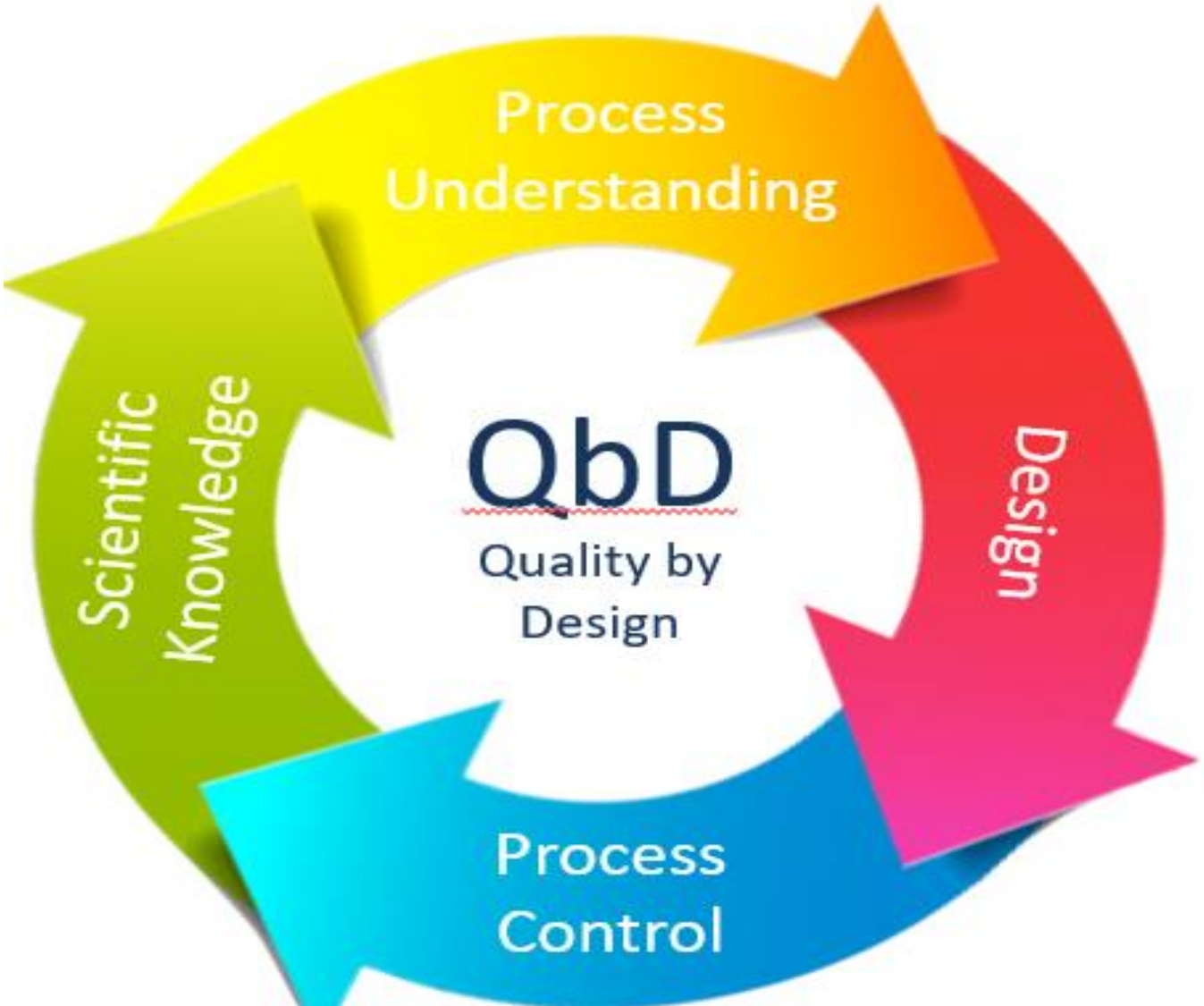
Quality By Design (QBD)



Quality

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

Quality by Test

Quality by Design

Quality by Design

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management

Significance Of QbD

- Quality by Design means –designing and developing formulations and manufacturing processes to ensure a predefined quality
- Quality by Design requires – understanding how formulation and manufacturing process variables influence product quality .
- Quality by Design ensures – Product quality with effective control strategy

QbD frame (in ICH docs)

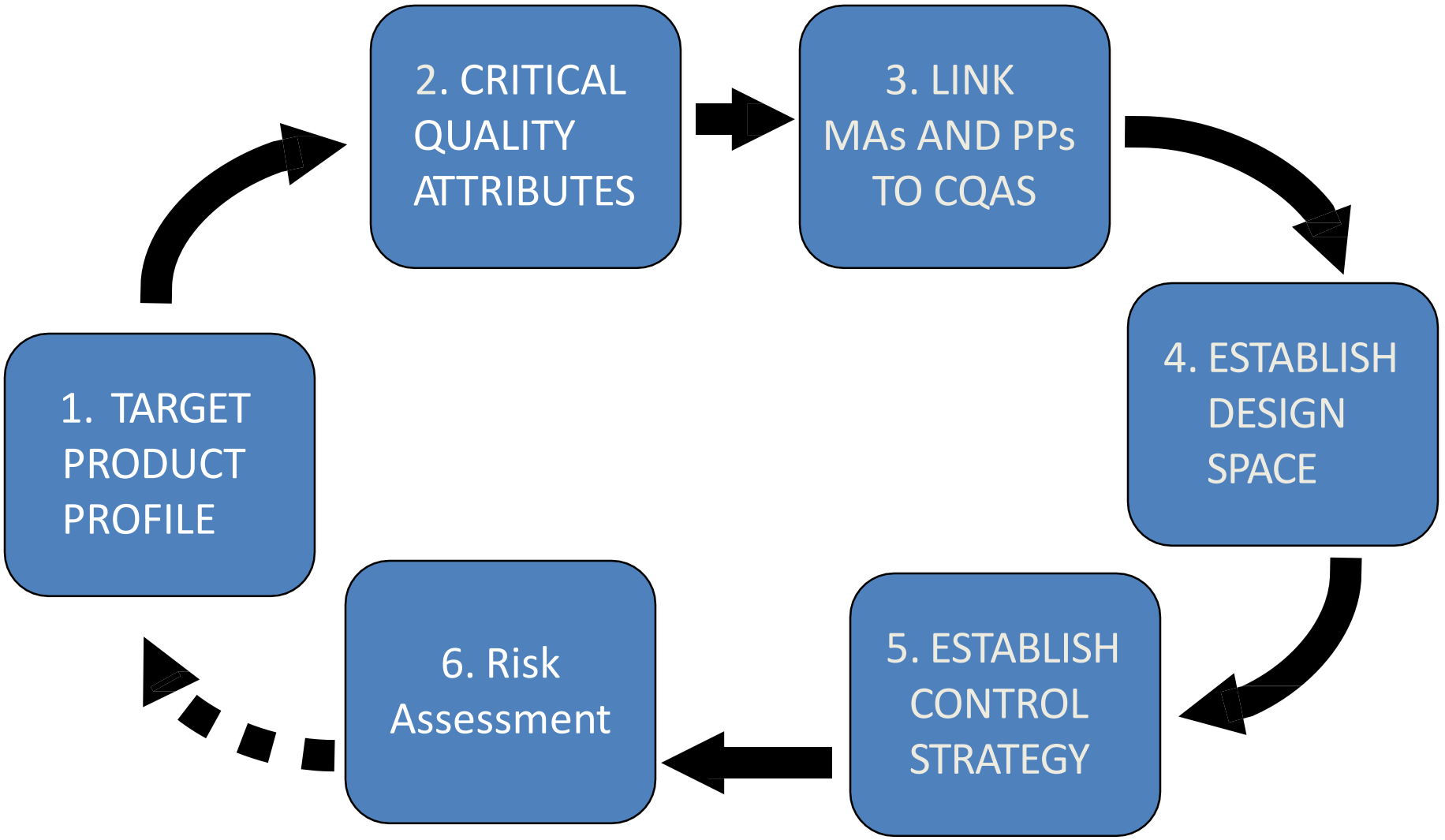
- The QbD frame contains concepts and tools - e.g. design space - to practice QbD in a submission file (design space approval).
- The selection of QbD implies the use of Quality Risk Management (ref.: ICH 9, Quality Risk Management) .
- The connection to a suitable (bio)pharmaceutical quality system offers opportunities to enhance science ad risk based submissions approaches

Quality by Design approach can be used for

- Active pharmaceutical ingredients
- Materials including excipients
- Analytics

- Simple dosage forms
- Advanced drug delivery systems
- Devices
- Combination products (e.g. theranostics)

What are the steps in a Quality by Design approach?

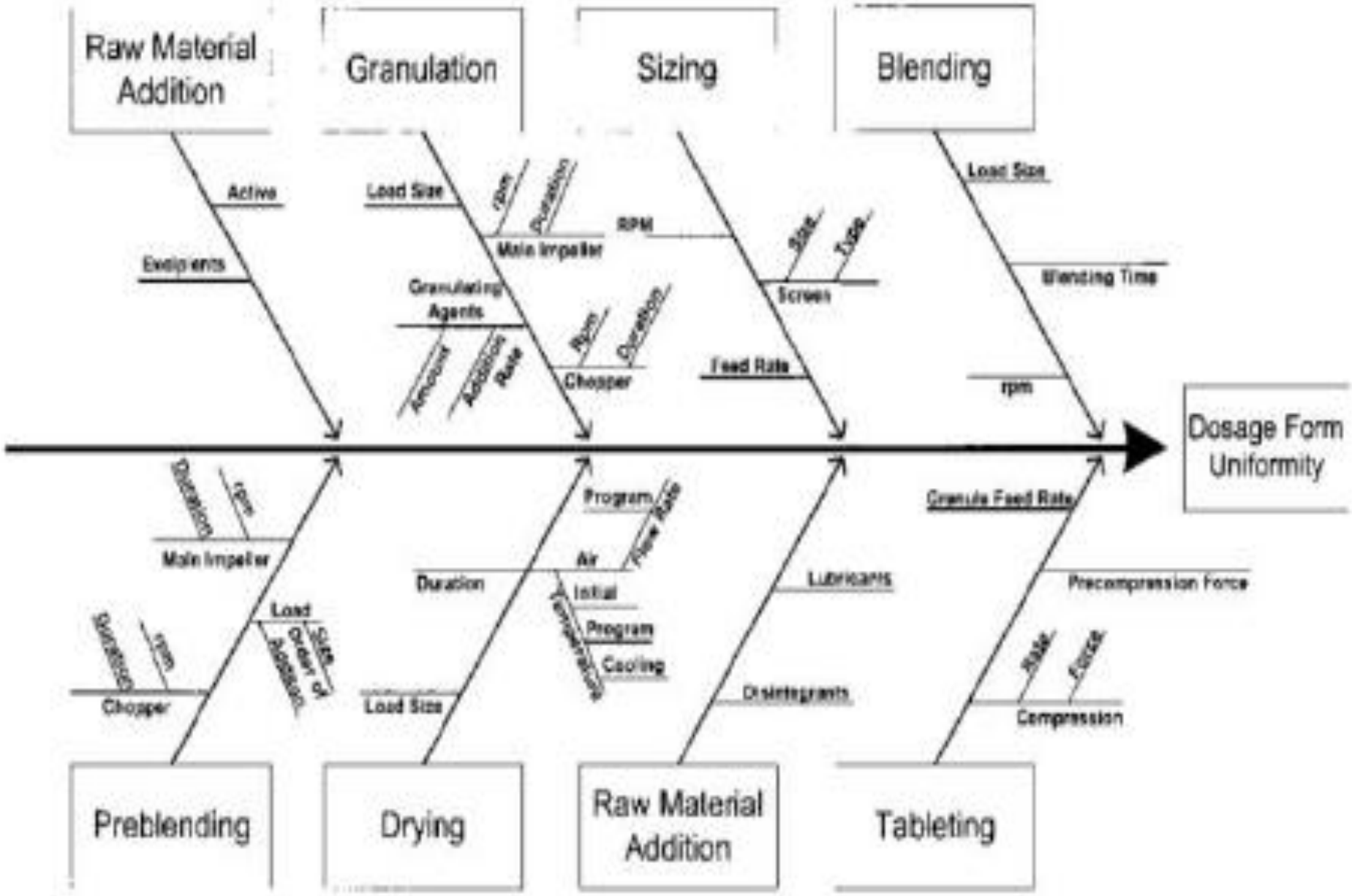


Target Product Quality Profile

- The target product profile (TPP) has been defined as a “prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy , of a drug product is realized”.

Critical Quality Attributes

- A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- CQAs are generally associated with the
  - Drug substance,
  - Excipients,
  - Intermediates (in-process materials) and
  - Drug product.


Raw Material Addition
Granulation
Sizing
Blending
Active
Load Size
RPM
Load Size
Blending Time
Granulating Agents
Screen
Feed Rate
rpm
Dosage Form Uniformity
Main Impeller
Program
Granule Feed Rate
Air
Lubricants
Precompression Force
Initial
Program
Cooling
Load Size
Disintegrants
Compression
Preblending
Drying
Raw Material Addition
Tableting

Material attribute

Material:

- Raw materials, starting materials, reagents, solvents, process aids, intermediates, apis, and packaging and labelling materials, ICH Q7A

Attribute:

- A physical, chemical, biological or microbiological property or characteristic

Material attribute:

- Can be an excipient CQA, raw material CQA, starting material CQA, drug substance CQA etc
- A material attribute can be quantified
- Typically fixed
- can sometimes be changed during further processing (e.G. PSD– milling)
- Examples of material attributes: PSD, impurity profile, porosity, specific volume, moisture level, sterility.

Process Parameter

- A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (Q8R2)
- CPPs have a direct impact on the CQAs
- A process parameter (PP) can be measured and controlled (adjusted)
  - Examples of CPPs for small molecule: Temperature, addition rate, cooling rate, rotation speed
  - Examples of CPPs for large molecule: Temperature, pH, Agitation, Dissolved oxygen, Medium constituents, Feed type and rate

Design Space

- Definition

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have beendemonstrated to provide assurance of quality

- Regulatory flexibility

Working within the design space is not considered a change

- Important to note

Design space is proposed by the applicant and is subject to regulatory assessment and approval

Design Space Determination

- First-principles approach
  - Combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering to model and predict performance
- Non-mechanistic/empirical approach
  - statistically designed experiments (does) ◦ linear and multiple-linear regression
- Scale-up correlations
  - Translate operating conditions between different scales or pieces of equipment
- Risk analysis
  - Determine significance of effects
- any combination of the above

Control Strategy

A planned set of controls,

- Derived from current product and process understanding,
- That assures process performance and product quality.

The controls can include

Parameters and attributes related to

- Drug substance
- Drug product materials
- Components, facility
- equipment operating conditions
- In-process controls
- Finished product specifications, and
- The associated methods and frequency of monitoring and control (ICH 10)

Risk Assessment

- Risk assessment : Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.
- Risk Assessment – A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

- Quality by Design define target product quality profile ,design and develop formulation and process to meet target product quality profile, Identify critical raw material attributes, process parameters, and sources of variability. PAT, DoE, and risk assessment are tools to facilitate the implementation of QbD. There is a need for vigorous and well funded research programs to develop new pharmaceutical manufacturing platforms.