Quality by design in Pharmaceutical Research

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ICH Q8 INTRODUCTION

This guideline is an annex to ICH Q8 Pharmaceutical Development and provides further clarification of key concepts outlined in the core guideline. In addition, this annex describes the principles of quality by design (QbD). The annex is not intended to establish new standards or to introduce new regulatory requirements; however, it shows how concepts and tools (e.g., design space) outlined in the parent Q8 document could be put into practice by the applicant for all dosage forms.

The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process.

QUALITY CONTROL

Quality has been given abundant significance by all regulatory bodies for manufacturing of pharmaceutical products and drug delivery systems.

Quality means customer satisfaction in terms of service, product, and process. Customer demands the perfection in quality, reliability, low cost and timely performance of the drug product.

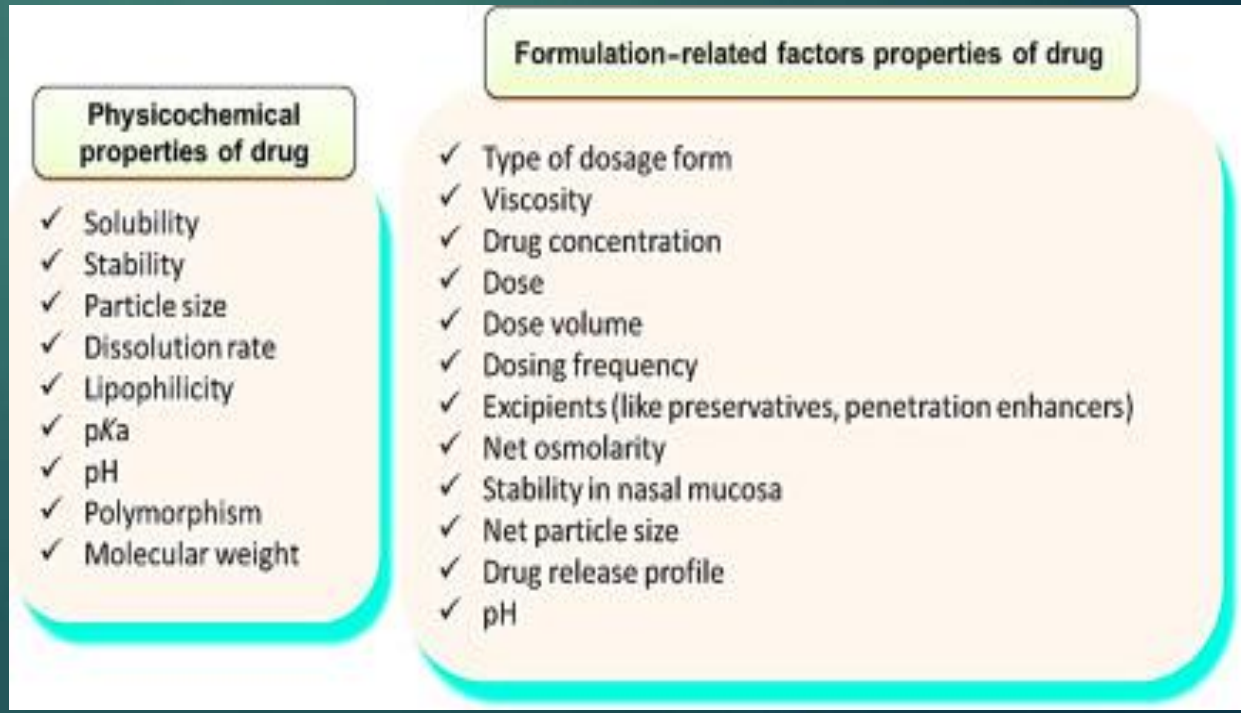
But merely analyzing the final product does indicate the quality; however it should be designed in the product

- **DRUG SUBSTANCES**

"The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability."

Examples of physicochemical and biological properties that might need to be examined include

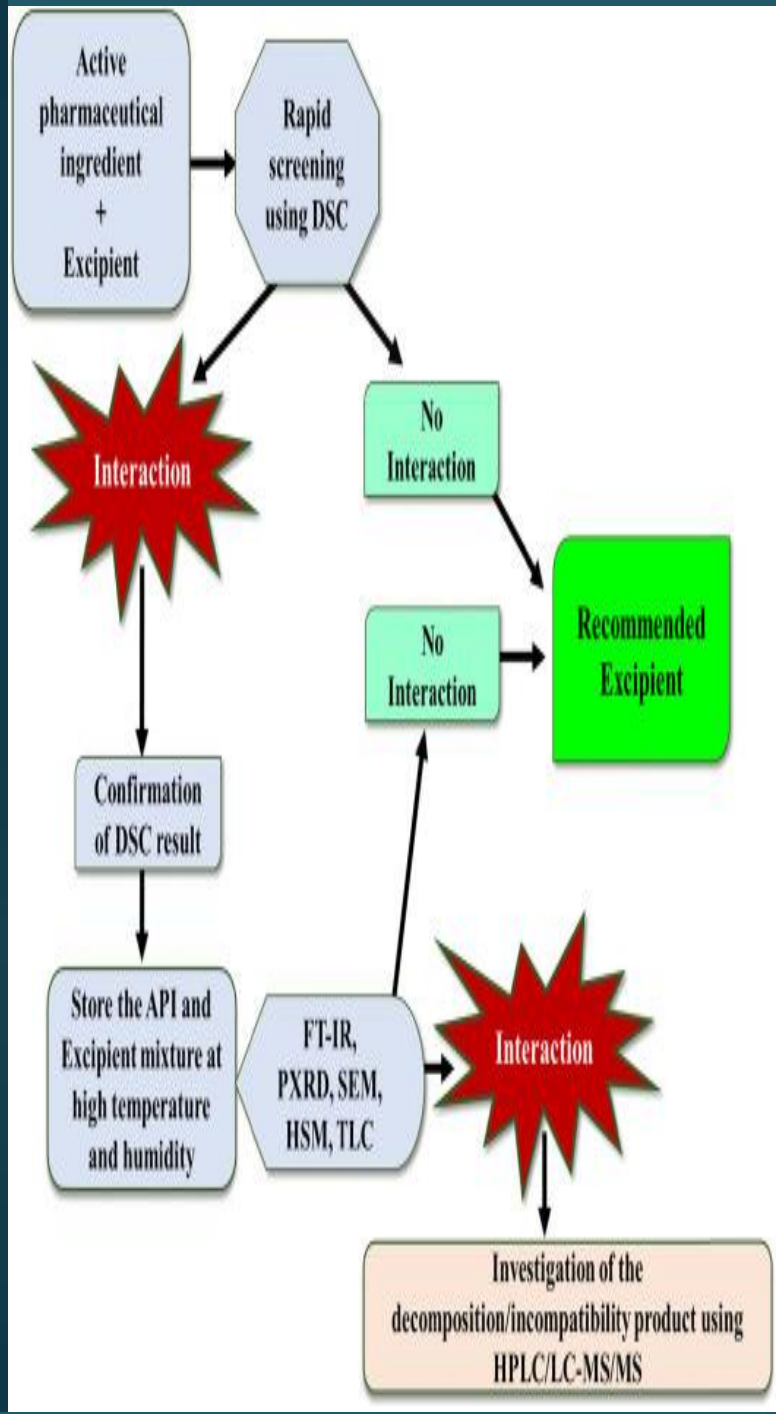
- Solubility,
- Water content,
- Particle size,
- Crystal properties,
- Biological activity,
- Permeability.



Study of drug and excipient

- The excipients chosen, their concentration, and the characteristics that can influence the drug product performance or manufacturability should be discussed relative to the respective function of each excipients.

- The compatibility of the drug substance with excipients should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated.



- A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product and also highlight the evolution of the formulation design from initial concept up to the final design.
- Information from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., BE) that links clinical formulations to the proposed commercial formulation.
- A successful correlation can assist in the selection of appropriate dissolution acceptance criteria, and can potentially reduce the need for further bioequivalence studies following changes to the product or its manufacturing process.

Parameters for correlations

SL. No.	*IN VITRO*	*INVIVO*
1.	Dissolution rate	Absorption rate (or absorption time)
2.	Percent drug dissolved	Percent of drug absorbed
3.	Percent drug dissolved	Maximum plasma concentration, C_{max}
4.	Percent drug dissolved	Serum drug concentration, C_p

Criteria for containers and closures

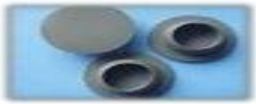
- The choice for selection of the container closure system for the commercial product should be discussed.
- The choice of materials for primary packaging and secondary packaging should be justified.
- A possible interaction between product and container or label should be considered.

- Different types of materials used for container

1. Glass container
2. Plastic container
3. Metal container


- Different types of materials used for closures

1. Rubber closures
2. Plastic closures
3. Metal closures


- Different types of materials used for secondary packaging

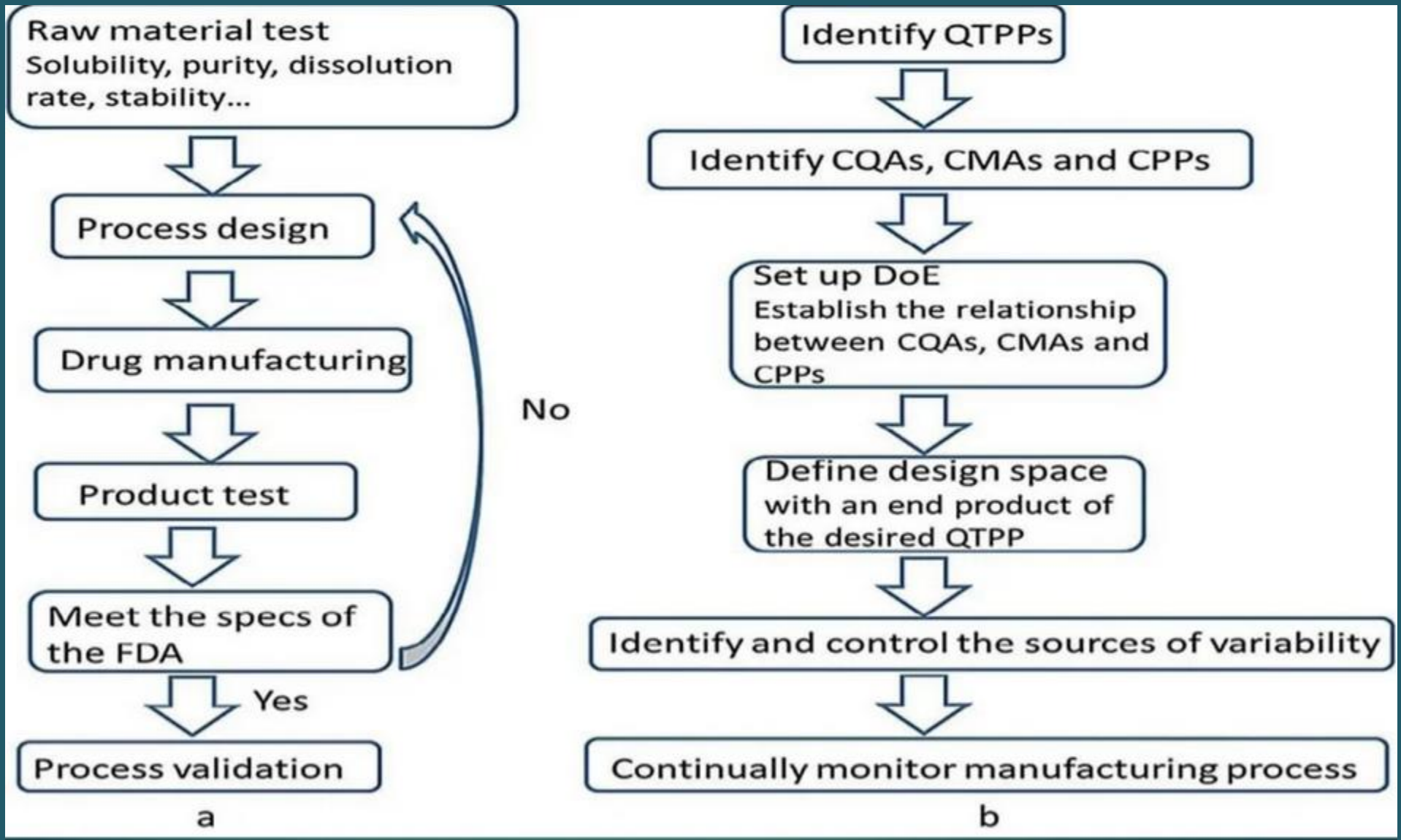
1. Paper
2. Cartons/cardboards


• MICROBIOLOGICAL ATTRIBUTES

➢ The selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial.

➢ For sterile products, the integrity of the container closure system as it relates to preventing microbial contamination.

➢ The lowest specified concentration of antimicrobial preservative should be justified in terms of efficacy and safety, such that the minimum concentration of preservative that gives the required level of efficacy throughout the intended shelf life of the product is used.



Comparison between QbT ***(a) and QbD (b). (QbT: Quality by Test; QbD: Quality by Design; QTPP: Quality Target Product Profile; CQA: Critical Quality Attributes; CMA: Critical Material Attributes; CPP: Critical Process Parameters; DoE: Design of Experiments).***

References

1. Guidance for Industry: Q8(R2) Pharmaceutical Development
2. Guidance for Industry: Q9 Quality Risk Management
3. Guidance for Industry: Q10 Pharmaceutical Quality System
4. Guidance for Industry PAT: A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance