



An Overview of Quality by Design for Generic Drugs

WHITE PAPER

Trends in Regulatory Outsourcing:

The regulatory agencies (USA, European Union and Japan) have made significant progress in implementing the concept of “Quality by Design” into its pre-market processes. ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) provide aid for manufacturers to apply Quality by Design into their own operations. Pharmaceutical Quality by Design (QbD) is defined as designing and developing formulations and manufacturing processes to ensure predetermined product quality. Quality cannot be tested into products; it must be built into products. Quality by Design assures in-vitro product performance which provides assurance of in-vivo product performance.



Description:

Tools of Quality by Design

- Design of experiments (DoE)
- Risk Assessment
- Process Analytical Technology (PAT)

Quality by Design is important because

- In product and process development for ANDAs Quality by Design (QbD) is becoming a most critical component. It is highly recommended to use the QbD approaches as part of product and process development strategies.
- The importance of QbD approaches during the technical review of an ANDA is increasing day by day, so it is essential that the understanding of the Office of Generic Drugs expectations by the generic industry.

The main objective of the generic pharmaceutical industry is ensuring the product quality. The generic industry follows the same concepts and principles set by the FDA, incorporating the concept of "Quality of Design" as core content in production and manufacturing. QbD is an important for generic manufacturers continue to produce high quality medicines for all consumers.

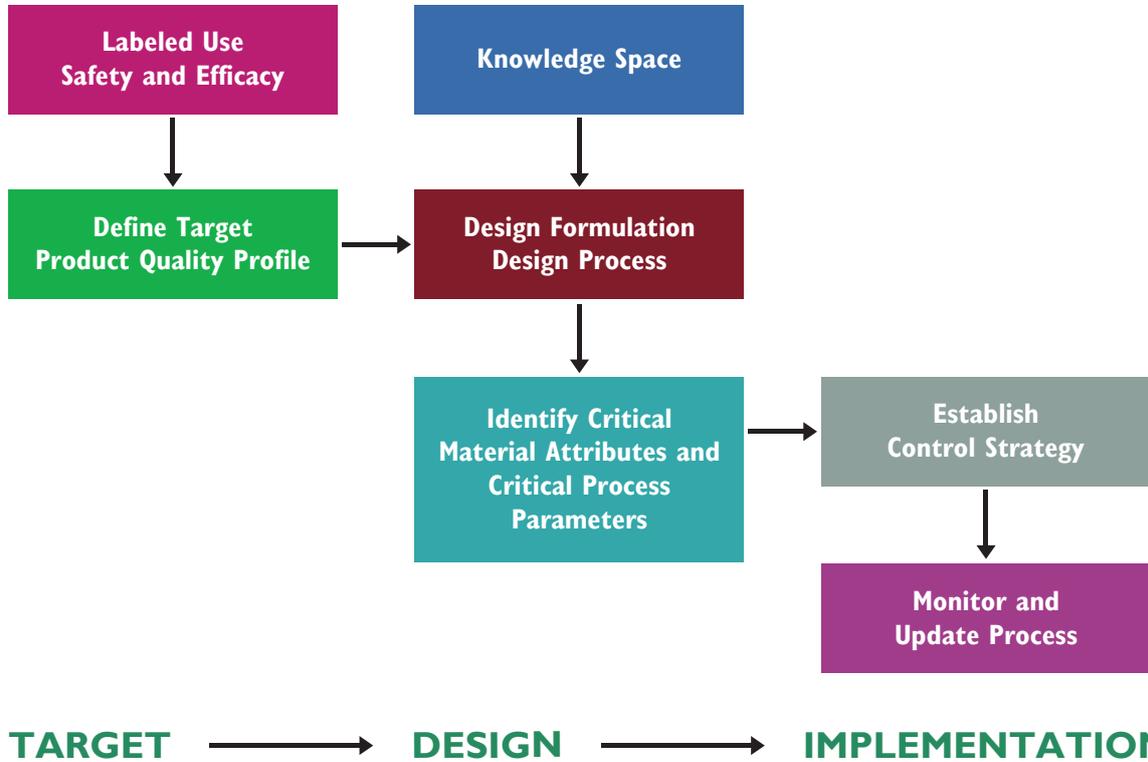
Quality is built into a product with a thorough understanding of the process by which it is developed and manufactured, and an intense responsiveness of both the risks involved in manufacturing the product and the best ways to decrease those risks. QbD provides the scientific structure to know all critical aspects of a drug formulation and manufacturing process. QbD enables to reproduce the highest quality product from batch to batch and year to year.

The variation between QbD for NDAs and ANDAs are at target product profile step i.e. for NDAs, TPP is under development whereas for ANDAs, the TPP is well reputable by the labeling and clinical studies conducted to support the approval of the reference product.

Design goals:

The following flow chart describes over view of Quality by Design:

Overview of Quality by Design



Target Product Profile (TPP): TPP states that overall intend of the drug development program and gives the information about the drug at a particular time in development. The pharmaceutical development contains identification of attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration through the TPP. The generic version and its reference product would expect to have the same TPP.

Target Product Quality Profile (TPQP): Pharmaceutical scientist translates the qualitative TPP into Target Product Quality Profile (TPQP) for further use in a Quality by Design Process. TPQP is a quantitative alternative aspect of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process. TPQP contains only patient relevant product information, it does not contain any specifications, it contains tests like stability, bioequivalence etc. which are not carried out for every batch.

Critical Quality Attributes (CQA): Determination of CQA is the next step after developing a QTPP in drug product development. CQA is an appropriate for attributes of the drug product. CQA are the physical, chemical, biological or microbiological properties or characteristics should be within the limit, range distribution to ensure the desired product quality. CQA includes product attributes that alter by changes to process parameters or formulation variables during pharmaceutical development that directly related to the safety and efficacy of the drug product. If any change in QTPP or CQAs directly impact on the product development report.

Formulation design, Manufacturing design and Development: At the laboratory scale the quality attributes of product manufacturing will be evaluated by the relevant ANDA sponsor can confirm the productive formulation. ANDA sponsors agree that a formulation design space would be valuable to industry if appropriate regulatory flexibility is grant. Process design is the first stage of process development which contains documentation of commercial scale

manufacturing process and scale up of manufacturing. The main factors considered for the process design and process development are facility, material transfer, manufacturing variations, equipment, QTPP and CQA. Preliminary feasibility studies may be necessary to conduct before completing the process development, it is depending upon the type of product development, type of process, and process knowledge. Physicochemical properties of the materials and excipients may influence the type of process.

Identification of critical process parameters (CPPs) and critical material attributes (CMAs): Manufacturing processes of pharmaceuticals contains a series of unit operations to produce the desired quality products. Material attributes are physicochemical or microbiological properties or characteristics of input or output materials. The output of the process depends on the process parameters and input material attributes. Process parameters include type of equipment settings, operating and environmental conditions (time, temperature, pressure, pH, speed and moisture).

In process- robustness studies are evaluated by effect of variations in process parameters and input material attributes. The limit on CMAs and CPPs are either scale independent (Design space) or scale dependent (Multivariate experiments) valuable. The process robustness studies are risk based because more studies are perform with complex products and fewer studies are perform with simple low risk dosage forms.

Risk assessment and design space: By performing risk assessment prior to the pharmaceutical development manufacturer has to decide which study to be conduct. By knowing which variables are critical and which are not by study results, can guide the establishment of the control strategy for in process, raw material and final testing.

Design space is a multidimensional combination and interaction of material attributes and process parameters which provides assurance of quality. Design space is a living document, which should be reviewed periodically as a part of quality system. Any change out of design space would be considered as a regulatory post approval change. Donna's Humpty Dumpty approaches to Design space is that Design space is the egg and Control space is the yolk. Design space determined at development level may not relevant to the commercial process. Therefore design space verification is essential at commercial scale.

Scale up and control strategy: Scale up is mainly based on general rule of thumb & trial and error approaches. During the scale up process, the process parameters vary but not the material attributes. Scale up with QbD can avoid the higher risk.

Control strategy defines in ICH Q8 (R1), specifically control strategy includes

- Control of input material attributes (Critical Material Attributes)
- Controls for unit operations (CPPs and Process end points)
- Product specifications
- In process real time release testing.
- In monitoring program for verifying multivariate prediction model.

Conclusion:

This article emphasizes the importance of TPP, TPQP, and CQA in QbD for pharmaceutical development. Identification of CMAs, CPPs provide links to product quality. Control strategy and design space are implementation of QbD elements into practice. Presently the QbD is becoming essential approach to the pharmaceutical quality.