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Short Communication

Quality by Design in Pharmaceutical Product Development

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The scientific approach to quality by design (QbD) in pharmaceutical product development is now a thrust area for the regulatory authorities and also the pharmaceutical industry [1,2]. It is proactive, scientific and risk mitigation based systematic approach to improve the quality standard of pharmaceutical product. Furthermore, it is a scheme for the development and manufacture facilitating approval of pharmaceutical products [3]. Early adoption and implementation of the concept by sponsors reduce the risk associated with product development during scale-up, manufacturing, and commercialization (Figure 1). Also, it facilitates product registration in key global markets thus bringing novel therapies to market faster. The utilization of QbD approach to the product development lifecycle can save their money through increase product and process knowledge, less rework and a smaller number of trials during research while also ensuring less deviation, less out of specification results and few products recalls post-manufacturing, thus promoting improved product quality and yield [4].

The concept of QbD originates from regulatory agencies guidelines for product registration to ensure safety and good quality medicines to patients, it is being widely adopted by pharmaceutical industries as a strategy to win regulatory approval and ensure successful pharmaceutical product development and commercialization. The QbD was first introduced in 2002 by the USFDA as a pharmaceutical quality initiative to reduce risk and enhance the quality of pharmaceutical manufacturing. Subsequent to this, the agency released a report "pharmaceutical quality for the 21st century: a risk-based approach" which noted QbD as a proven scientific approach to ensure safety and efficacy of medicines to patients [5,6].

Figure 1: Schematic diagram of pharmaceutical product development steps according to quality by design.

In 2013, the FDA mandated QbD implementation throughout the product and process design elaborating elements of QbD such as quality target product profile (QTPP), critical quality attributes (CQAs) and critical material attributes (CMAs). Recently, important global regulatory agencies – including the FDA, the European Medicines Evaluation Agency (EMEA), Japan's Pharmaceutical and Medical Devices Agency (PDMA) and the Korean Ministry of Food and Drug Safety (MFDS) seek evidence related to QbD implementation in product dossiers during development, so as to ensure product quality during approval [7]. The element of pharmaceutical product development by QbD includes:

1) **Quality-target product profile (QTPP):** QTPP includes the desired target profile or specifications based on quality attributes and the market requirement for the product to ensure safety, efficacy, quality and patient compliance.

2) **Critical material attributes (CMAs):** CMAs of the active ingredient and excipients intended to be included in the formulation. Each excipient in the formulation has a specific role or functionality which contributes to product performance. Hence the CMAs of each excipient must be identified and monitored closely for the batch to batch consistency so that the functionality is not altered and the final product performance is not impacted. This should also be complemented with the thorough investigation of the literature of the active pharmaceutical ingredient, including the various physiochemical parameters such as pKa, partition coefficient, solubility, permeability, developmental classification system class, photostability, degradation kinetics, absorption, distribution, metabolism, and elimination all of which greatly influence its performance.

3) **Design of the experiment (DOE):** DOE is planned, during formulation development considering all the independent factors and the dependent factors so as to statistically arrive at the optimum formulation. The independent factors or variable includes various labels of excipients high, low and medium. The dependent factor includes all the desired quality attributes within the specification range. This also helps to establish a design space for the final formula with desired quality performance to ensure a safe and robust product. DOE is also planned during process optimization to establish the optimum range for all critical process parameters (CPPs) including process temperature, speed, and time etc. Alternatively, both the formulation and process parameters can also be optimized through one DOE at research and development (R&D) stage. However, the working range for all critical parameters must be reconfirmed during scale-up or validation batches for exhibit or commercial batch size. The holistic idea about implementing a DOE to arrive at an optimum formula or process is to derive conclusions statistically with the minimum number of trials, thus saving both time and cost incured during product development.

4) **Failure mode effect analysis (FMEA):** FMEA is done before scale-up of the pharmaceutical products. The relative risk ranking is done and high-risk factors are reduced to medium or low and low-risk factors are mitigated through appropriate controls set for each high or medium risk factors.

5) **Critical quality attributes (CQAs):** The CQAs and their requirements evaluated and inferred during product development are finalized and submitted to regulatory agencies as the finished product specification intended for the exhibit batches and commercial batches release and shelf-life. This ensures a consistently good quality product with optimum performance.

It is to be noted that specifications and requirements of some of the key quality attributes during release and shelf-life is to be reconfirmed and aligned closely with the pilot and pivotal bioequivalence study batches, especially the drug release profile. For modified release products the percentage drug release profile for each time point in the specification must be supported with the *in-vivo* and *in-vitro* co-relation studies. The quality control media must be bio-relevant with substantial proof to indicate and differentiate good and bad quality formulation. The analytical methods must be validated and stability indicating to ensure adequate purity of the drug and absence of impurities. The pharmaceutical companies benefit from implementing QbD in numerous ways including meeting bioequivalence and clinical trial timelines, effective utilization of time and resources, faster product approval and registration, as regulatory agencies look for QbD elements, continuous process improvement, reducing manufacturing issues, challenging bad methods or processes, sharpened focus on procedures, quicker batch release and stability study generation, faster commercialization through the ability to scale up with no inherent defects and consistent sustained processes that can be 'Right First Time' [8].

The worst-case scenario for not implementing QbD early enough can mean going back to start of formulation development after learning a formulation cannot be manufactured consistently. This causes wastage of time, money and resources [9]. Many companies choose to bypass QbD investment in the early development of a new chemical entity (NCE) by using fit-for-purpose tablet formulations or blend in a capsule formulation for faster clinical trials. While this initially saves time, it may lead to later discoveries about product robustness and efficacy that shall compromise the product quality. As indicated to pharmaceutical companies by the global regulatory agencies to evolve from good manufacturing practices to filing more data on product quality by design during drug application, it should be holistically implemented by every pharmaceutical company including biopharmaceutical companies during the development of small and large molecules [10].

The QbD provides a distinct advantage during the regulatory filing from patient safety and sponsor's technical competency. To reach its full potential to completely de-risk the drug product development lifecycle, QbD must link early- and late-stage development with manufacturing and commercialization.

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