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EDITORIAL

Quality by Design (QbD) in Product Development Life Cycle: Retrospect and Prospects

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In an endeavour to improve patient efficacy, safety and quality of drug products, a noteworthy element of risk has always been experienced during their therapeutic usage, invariably due to their inadequate or inconsistent quality. Development and manufacturing of varied drug products, accordingly, is an arduous task today, confronted with numerous patient-centric requirements and regulatory challenges.

Since decades, adoption of systematic approaches in several technology-driven industries has successfully been yielding diverse products marked with robust quality, enhanced resource economics and improved process capability. With the growing concern and criticism for addressing the pharmaceutical quality standards too, the International Council for Harmonization (ICH) instituted a series of guidance documents in the last a few years, especially Q8 to Q14, all emphasizing use of rational principles of Quality by Design (QbD), directly or indirectly. Subsequent endorsement of such judicious QbD paradigms by key regulatory agencies, like USFDA and EMEA, offered unequivocal testimony to the immense significance of such paradigms for potential stakeholders, viz. patients, industrial scientists and regulators.

Pharma QbD is verily a systematic science- and risk-enabled strategy that focuses on evaluating, understanding, refining and ensuring quality throughout the development and manufacturing of a drug product. Beginning with pre-defined objectives, QbD accentuates on product and process understanding, based upon sound science and quality risk management (QRM). Implementation of QbD principles, therefore, not only tends to unearth the scientific minutiae during systematic product development, but also leads to improved time-to-market, enhanced knowledge-sharing, limited product recalls and rejects, reduced post-approval changes, and efficient regulatory oversight.

One of the integral tools in the QbD armamentarium is Design of Experiments (DoE), employing apt usage of experimental designs. Amidst a multitude of plausible interactions of the drug substance(s) with a plethora of functional and non-functional excipients and processes, the DoE methodology targets to attain the breakthrough systems with minimal expenditure of time, developmental effort and cost. Such approaches are far more advantageous, as these require fewer experiments to achieve an "optimum" formulation, make problem tracing and rectification quite easier, reveal any drug-excipient-process interactions, simulate the product performance, and comprehend the process behaviour, in order to facilitate superior formulation development and subsequent scale-up.

The overall QbD-based philosophy revolves around meticulous drug product development initially by defining the quality target product profile (QTPP), identification of critical quality attributes (CQAs), critical material attributes (CMAs) and critical process parameters (CPPs), apt choice of experimental designs, precise definition of design space, and embarking upon the selection of "optimum" formulation. Prioritization through selection of "vital few" input variables is often accomplished through the QRM studies via earmarking the severity of risk, frequency of its occurrence and detectability associated with each input variable, through extensive brainstorming exercise among the team members. Factor optimization studies and model fitness studies are next conducted to discern the optimal "design space". Subsequent to QbD validation exercise, the product or process is scaled-up through pilot-plant, exhibit and production levels in an industrial setup to ensure product reproducibility and robustness. An explicit and versatile "control strategy" is immaculately postulated for "continuous improvement" for accomplishing superior quality of the finished product.

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QbD is an inimitable quality-targeted approach for developing efficacious, cost-efficacious, safe and robust drug products, generic as well as branded. On industrial fronts, a formulation scientist can derive its stellar benefits at every stage of product development lifecycle, and beyond, even after commercial launch and post-marketing surveillance. The pivotal applications of Pharma QbD encompass:

Formulation by Design (FbD)

Product and process understanding are the twin keystones of FbD, a cliché specific to QbD application in rational drug formulation development. FbD requires holistic envisioning of the formulation development, including how CMAs and CPPs tend to impact CQAs in laboratory, during scale-up, and final production of robust drug products. Defining such relationships, between these formulation or process variables and quality traits of the formulation, is almost an impossible task without the application of apt FbD models. More the formulator knows about the system, the better he can define it, and the higher precision he can monitor it with.

Analytical QbD (AQbD)

On the heels of QbD, AQbD endeavors towards understanding the predefined analytical objectives. These comprise, quality target method profile (QTMP) of an analytical method, and identifying the critical method variables (CMVs) affecting the critical analytical attributes (CAAs) for attaining enhanced method performance, like high robustness, ruggedness and flexibility for continual improvement within the ambit of analytical design space. Besides, AQbD facilitates attaining flexibility in the analysis of API and impurities in dosage forms, stability samples and biological samples, to go beyond traditional procedures of method validation. Like FbD, the AQbD also embarks upon risk-assessment studies and DoE-guided optimization studies for attaining the superlative method performance.

Manufacturing Process Design and Validation

QbD can also be used to design and validate a pharmaceutical manufacturing strategy, resulting in consistent product performance. This includes understanding the impact of CPPs on CQAs, identifying and mitigating sources of variability in the process, and monitoring the manufacturing process to ensure that it is operating within the design space.

Drug Delivery and Analytical Laboratory Research

The realm of novel drug delivery has endowed a newer outlook towards product development and consequent patient therapeutics. Nanostructured systems, in particular, tend to exhibit stellar benefits, including enhanced surface-area-per-unit volume, improved solubility, target-specificity, controlled-release potential, biocompatibility, stealth characteristics, precise control of particle size, and also, augmented bioavailability. Formulation development of such nanostructures, nevertheless, involves extensive resources and intricate phenomena. Rational formulation development of such nanopharmaceuticals during laboratory research is, thus, possible only using apposite FbD strategies. Likewise, analytical method development and validation research using AQbD paradigms is the need of the hour in laboratories not merely to arrive at optimal analytical solutions, but to furnish deeper analytical understanding of the concerned chromatographic process too.

Other QbD Applications in Product Life Cycle

QbD not only facilitates comprehension of products or processes or establishes design spaces, but also helps in attaining pharmaceutical excellence and federal compliance with phenomenal ease and economy. Hence, besides the drug formulation development and analytical method development, the concept of QbD has steadily been percolating into other diverse interdisciplinary areas too like API development, herbal drug extraction, pharmacological evaluation, dissolution testing, bioequivalence trials, and stability testing.

The merits of QbD techniques are galore and their acceptability upbeat. Putting such rational approaches into practice, however, usually involves considerable mathematical and statistical intricacies. Today, with the availability of powerful and economical hardware and comprehensive QbD software, the erstwhile computational hiccups have been greatly simplified and streamlined. Popular computer software packages available to steer the scientists at various step during entire product development cycle include, JMP®, Design-Expert®, Minitab® and MODDE®.

In a nutshell, the QbD paradigms require meticulous envisioning of the product development lifecycle as a whole, starting from laboratory to commercial scale via pilot plant scale-up transitioning, to produce robust and stable drug products. As variability tends to exist at every stage of product development life cycle, application of QbD needs to be omnipresent too. QbD promotes a culture of quality excellence through continuous improvement, leading eventually to improved patient outcomes and increased regulatory compliance. In fact, QbD has been a boon to accelerate the product development process, expending minimal efforts for producing maximal performance. Today, the federal agencies look for patient-centric quality as "built-in" into the system. In this regard, the utility of QbD tools and techniques, as the quality-enabler in developing optimal drug products meeting requisite high product quality during myriad stages of development, leads research mindsets to evolve "out-of-box" strategies too. The practice of systematic

QbD implementation for products has undoubtedly spiced up over the past a few decades, yet it is far from being accepted as a standard practice. Albeit the federal regulations for generic drug products are already in place, further initiatives need to be undertaken to inculcate regular use of QbD paradigms for their holistic implementation in different facets of product life cycle. Besides, the synergistic use of in-process non-invasive Process Analytical Technology (PAT) and Real-Time Release Testing (RTRT) tools, in tandem with process engineering approaches like extensometry and chemometrics, can also help in ameliorating product and process understanding and augmenting the process capability for efficient manufacturing. Notwithstanding enormously augmenting popularity of QbD paradigms in the systematic development of robust formulations, drug substances and analytical methods, concerted initiatives need to be undertaken to draw apt attention of all stakeholders for harvesting ample benefits of such rational approaches. Let appropriate and adequate exposure to QbD training be provided to the young enthusiasts in the institutional set-ups, to pave the way for delivering the product development excellence as well as hassle-free regulatory compliance, while they serve the industrial set-ups.

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