QbD not QED

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The quality of a product manifests itself by various attributes, such as, its ability to adequately fulfill the function for which it was built or manufactured, consistency of performance and stability throughout its shelf life, user friendliness, and being possessed of an intuitive and multi-functional design capable of being adapted to as wide a range of operating conditions and/or user requirements as possible.

The formalization of a process that defines, identifies and quantifies risk, and evaluates its mitigation through the establishment of a 'design space' and associated control strategy will be beneficial to pharmaceutical manufacturing operations. The formal risk assessment and mitigation protocols, as part of the Quality by Design (QbD) process, inherently lend themselves to the identification of a design space, the factors that influence it and its operating limits. The QbD paradigm ensures that personnel have knowledge of why the critical process parameters (CPPs) and the critical material attributes (CMAs) have specific values, the limits of its workability and the flexibility to change within the 'design space' without affecting the critical quality attributes (CQAs) of the product.

QbD ensures that manufacturing processes can be scaled up and transferred to different production sites with a greater probability of success. It has the potential to make processes less dependent on exquisitely specific equipment and equipment specific operating parameters. Technology transfer is therefore made more 'nimble' and faster due to the possibility of manufacture using different equipment and operational configurations that typically exist across multiple manufacturing locations, so long as those configurations keep the CPPs within their design specifications.

From the regulatory point of view, QbD complements good manufacturing practices (GMP), so that processes can be scrutinized with the assurance of added safety margins. Operating conditions can be changed across plants or locations within the design space without the regulatory burden of additional or supplemental filing.

QbD also provides a way to incorporate CMAs that significantly influence the CQA of the product yet are not compendial tests or requirements. It identifies the need for setting internal (non-compendial) specifications for

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those attributes of the raw material depending upon the process and/or formulation application. Compendial specifications are designed to establish the identity, purity and safety of the raw material. QbD requires that the formulation scientist be prepared to go beyond the monograph specification and determine which material attributes, including non-compendial attributes, are critical for the successful manufacture of the product. Excipient users should realize they cannot rely solely on compendial specifications as the only means to 'qualify' the raw material for different process/product applications.

Attempts to systematize knowledge can only go so far. This is because, while processes and CQAs may be quite 'generic', the way they influence (or are influenced by) different formulations containing different APIs and excipients is very specific (different). For example, the unit operation of steam sterilization will not be expected to work in a similar way for non-viscous and viscous formulations and the pH may be influenced differently by APIs that exhibit different ionization constants, isoelectric points and aggregation profiles within the context of the formulation composition. QbD cannot be used to conceive and design process blueprints, it can only be used to establish and optimize the design space of unit operations that make up those processes. QBD presupposes, and is not a substitute for, a thorough knowledge and under-standing of physical chemistry, organic che-mistry, materials science, process engineering, together with experience and judgement. No amount of QbD can salvage a process that is not operating in an adequate state of control *vis a vis* the appropriate process capability (C_{pk}) and six sigma descriptors. Such a process may be poorly designed in the first place and QbD is unlikely to succeed without going back to the basics and redesigning the process. Automation of QbD using the design of software (DoE) experiments can therefore be expected to proceed to a point, but no further, not only because of differences in 'design space' but also differences in design surfaces, the possibilities that the design space does not encompass the optimum in the first place and that the design space is discrete (not continuous) with regard to one or more CPPs. It is tempting to draw an analogy between the "auto-pilot" software that can control an airplane, but cannot take off and/or land it without human intervention.

QbD is a useful tool to identify CMAs and CPPs that, in turn, make for robust processes. A large part of the QbD deliverable is based on designing experiments that study the effect of multiple variables on multiple CQAs via a DoE. The seduction of (mis)application of DoE to formulation or process development arises because of:

1. The (mistaken) notion that the CPPs are algorithmically compressible, and follow continuous (as opposed to discrete) patterns/functions that can always be described using mathematical equations.

2. The (mistaken) notion that unit operations comprising a process can be mathematically linked, so that cause and effect relationships apply not only within, but across multiple unit operations.

3. The (mistaken) notion that an expansion of the design space either affects only some CPPs (without any effect on others) or affects all CPPs in a mathematically monotonous way, so that an apparent design space expansion is always concurrent with increased C_{pk}.

4. A drive to reduce development costs, propelled by the (mistaken) propensity to believe that automation of process development and design is possible and can be achieved by simply performing the 'mix and match' experiments dictated by the DoE software and recording their effects on preselected CQAs.

The misapplication of QbD for purposes for which it was not intended for is unwise and

likely to be counterproductive. It would be a shame if, by virtue of such misapplication, the QbD paradigm were to be maligned or abandoned, because there is no denying that it does bring added value to pharmaceutical manufacturing processes. Ill-conceived and/or improper application of QbD, including any that treat pharmaceutical processes as "modular" and being totally mathematically patterned, must be curbed. The proper application of QbD to establish and optimize the 'design space' of thoughtfully developed (i.e. grounded in a sufficient knowledge and understanding of physical and organic chemistry, materials science, process engineering together with experience and judgement) formulations and processes should be increased, so that its full potential may then be realized.