Why is it that QbD in its current form will not help in improving the quality of products (tablets/capsules), and what may be done about it?

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This article presents a practical view on QbD (Quality by Design) approach and its implementation. It is argued that, the critical component of the approach, the defined "quality" attribute to be achieved is lacking. To address this issue, from the consumer/patient perspective the quality of a tablet/capsule product may be defined as availability/release of the drug in an expected amount and manner. However, the technique most often used (known as drug dissolution testing) to evaluate such quality has been recognized to be flawed. Therefore, it is highly unlikely that the QbD approach as presented will be successful in providing improved quality of the products. Suggestions are made for addressing the issues for a potentially successful implementation of the QbD practice.

QbD is not a new or complicated concept or practice. In essence, the concept is based on a simple philosophical approach that if one would like to produce an item successfully and efficiently, it is much better to approach for its production, in a systematic way. The systematic way suggests that a production process should be considered a composite of multiple small individual processes. The systematic way or QbD emphasises the fact that if these individual steps/processes are understood, optimized and controlled adequately then not only manufacturing will become efficient but deficiencies in the processes can be detected and corrected easily and efficiently. The concept is quite generic and should be applicable in most, if not all, cases of manufacturing and production.

The question is, if it is a systematic way of manufacturing/production then why is it called quality by design or QbD? Why are the words "quality" and "design" used? The reason is that manufacturing in itself is not the end, but is a "tool" or "process" for the end which is to produce quality products. That is, one sets an objective or standard to manufacture a quality product and then design (systematic way) the process/manufacturing to achieve the quality product.

Let us suppose that we want to produce sugar having 95% purity with ±1% variation. This will be our quality standard and we should design manufacturing systematically with the knowledge and understanding of the small or individual processes to achieve this goal (purity or "quality"). If a batch shows test results outside the limits, then the product will be considered of substandard quality and the process needs to be corrected to bring the production within limits.

Now let us consider that for certain specific reasons, we require sugar of 99% purity with ±0.1% variation, which can be achieved with higher standards of production. The product described above, though met its quality objective becomes inferior for this particular requirement. In other words, quality becomes a subjective term and ***must be set or defined first before one tries to achieve it or manufacture the end product***. For achieving the quality product, in addition to manufacturing, one must also require an analytical method to establish and/or monitor the quality. If one already has an analytical method which was used for production in the earlier example with sensitivity of 0.1% variation or better then there is no need to develop a new method. However, if the available method has sensitivity lower than 0.1% then for the second product, even before one starts manufacturing the product, ***one has to have an appropriate analytical method with the required sensitivity***.

Now let us consider that we like to produce syrup of sugar, which should have a concentration or strength of 100 gm/100 mL of sugar in water with a variation of 10 gm/100 mL. There is another requirement for the syrup that the sugar content must not crystallize out at room temperature for at least three months. In this case, quality is not only defined by content (which is somewhat relaxed compared to the earlier examples) but also based on the stability of syrup (i.e. shelf life). Therefore, some sort of solubiliser or stabilizer may be required to achieve this quality expectation.

The point being that this quality aspect is a subjective in nature and it changes with products and specific needs. Therefore, to establish or follow QbD, the first and foremost condition is to define the requirement or "quality" i.e. what is to be achieved.

Now let us move on to the pharmaceuticals side. For the purpose of this article, discussion is restricted to tablet and capsule products only. If one would like to have a quality product, what would it mean? Should the drug content of the product be 90%, or more? Should the

content variability product-to-product, batch-to-batch or unit-to-unit be 10, 5, 1, 0.1%. As the product is an oral dosage form (tablets/capsules) then should there be requirements for the drug delivery aspect i.e. should the drug be delivered within minutes or hours? In addition, are the required analytical methodologies available to establish the quality requirements or standards? Let us say that we like to have a tablet product with 95% drug content with a variation of 5% which will be capable of delivering/releasing its entire drug in 30 minutes with 10% variation in release time. If we have a product which meets the indicated conditions, then we will consider it a quality product, i.e. quality target, all other things being equal.

Now the quality requirements are set and these requirements will be transferred for product development and manufacturing. Based on different combination/permutations (i.e. variables) of ingredients/manufacturing, one is to come up with the most appropriate setup ("design") to produce the product having the required quality of the product in an efficient way. As there can be numerous variables, however, based on expertise and experience one decides the most critical variables and evaluate their impact on manufacturing. Here, rather than trying different combinations or variables individually, it may be helpful to design the study (experiment) in such a way that multiple parameters could be evaluated simultaneously. This simultaneous evaluation of the impact of different variables is called design of experiment (DoE). This exercise may be based on statistical analysis thus participation of a statistician may be helpful. It is important and critical to note that the use of statistical design is often considered optional and may not be necessary at all for simple product development and manufacturing steps.

Note that DoE and its related statistical analyses are tools to evaluate and establish the impact of different variables for achieving the desired endpoint i.e. "quality". This quality requirement is usually set by the end user, e.g. physician, clinicians or consumer, which formulators/manufacturers try to achieve using different tools, one of them is DoE or QbD. It is exactly like an analytical chemist (e.g. chromatographer) tries to select an appropriate combination of column/medium and sample clean-up procedure to achieve an appropriate analytical method having a required sensitivity so the quality of a product can be established and monitored.

The question is why has the QbD concept or practice become a popular topic in the pharmaceutical area? The popularity is based on an assumption that an unexplained and presumed lack of "quality" needs are to be corrected or enhanced, as explained below:

It is generally recognized that even if a product contains the expected amount of drug but that the drug is not releasable in an expected manner then the product becomes of substandard quality. Therefore, the only criterion one is required to establish the "quality" of tablet/capsule product is the assessment of drug release characteristics of the product, ***because drug content estimation becomes part of the release test as well***. This drug release characteristic is commonly known as drug dissolution characteristic. Thus, there is a requirement for dissolution test for such products. This assessment of dissolution can be done in vivo (by bioavailability/bioequivalence studies in humans) and in vitro (by drug dissolution testing). Considering cost and time constraints and ethical reasons human studies are conducted on limited basis. On the other hand, in vitro dissolution testing is heavily relied upon for the evaluation drug release characteristics of a product thus "quality". It is to be noted that there is ***no*** alternative available at present but to conduct drug dissolution tests for quality assessment of these products.

Drug dissolution tests are conducted using commonly available dissolution testers based on experimental conditions mimicking a human physiological environment, because this is where the product is expected to release the drug for its absorption in the body and to result in its therapeutic effect. As stated earlier, the dissolution test is of critical importance, however, formulators, analysts, manufacturers and regulators have been thoroughly frustrated with the outcome of dissolution testing. The reason being, the test results are often highly variable and unpredictable. Unfortunately, this variability and unpredictability is generally attributed mistakenly to the product manufacturing itself. Thus, a view has been formed that perhaps pharmaceutical manufacturing is not based on sophisticated and appropriate designs using QbD principles, such as statistical DoE, that may be causing the poor quality of the product. It is to be noted that there is a serious lack of substantiated evidence showing that the poor quality of the product, if it exists, is due to the poor manufacturing, its design or lack of statistical analyses. The introduction of QbD concept/practice into the pharmaceutical domain is based purely on the assumption that pharmaceutical products are of poor quality and, unlike other industries, the pharmaceutical industry is not using modern QbD principles thus resulting in poor quality products. This view appears to

form the basis for the introduction of the QbD practices in the pharmaceutical industry.

On the other hand, if one critically evaluates the issue of observed variability and unpredictability of test results, extensive experimental evidence clearly points toward the flaws of the dissolution technique. The only tool available at present to quantify the quality, during product development, manufacturing, and for QC purposes, is the drug dissolution test. This test has been extensively used for the past many decades, unfortunately however, it has never been qualified and validated for its intended propose i.e. evaluation of drug release/dissolution in humans. Frustrations have always been with this test. Recent studies categorically have shown flaws in the testing and the apparatuses, concluding that apparatuses and testing have to provide the observed high variability and unpredictability in results and lack of their physiologically relevancy. Therefore, if the analytical methodology is flawed, then there is no possibility of ascertaining the quality of the pharmaceutical products, even with the use of QbD approach. It is important to note that, contrary to common and strongly promoted belief and desire, implementation of QbD will not be possible without having a reliable and relevant analytical methodology which in this case is drug dissolution testing.

It is often argued that if individual components/processes during manufacturing are optimized and controlled sufficiently then the use of the analytical method (e.g. dissolution testing) can be circumvented. This is simply a weak and invalid argument.

It is also often stated, in support of the concept of QbD, that the concept is based and focus on the requirements and needs of the consumer (patient). However, from this perspective, it can be argued that the consumers needs do not require manufacturing based on the QbD approach, consumers needs are met by providing the product capable of delivering expected (labelled) amount drug with high consistency (low variability). It is immaterial for the consumer if the product has been manufactured using QbD (with its statistical designs) or not. From the consumer perspective, the need can only be filled if it is shown that the product will deliver the expected amount drug and in the expected time, which can only be established and monitored by drug dissolution testing.

As stated above, the currently used dissolution testers are not validated and qualified testers, therefore one cannot ascertain quality of the product, at present. Therefore, it is worth repeating that if quality of product is to be improved, one must first have to define the "quality" and then to have a reproducible and reliable analytical methodology (dissolution testing) to establish this "quality". The application of QbD comes after as its success is dependent on the availability of appropriate analytical methodology.

Recently, a new dissolution tester based on a crescent shape spindle has been suggested considering the physiological aspect of human GI tract physiology (link). In addition, a simple mathematical approach has also been suggested for the estimation of plasma drug levels from drug dissolution results (link) which is an essential requirement in assuring "quality" from consumers' perspective. The use of this approach may provide a missing link for successful implementation of QbD.

In conclusion, QbD is a systematic approach which may be used for developing and manufacturing of quality products. However, for its successful implementation a quantifiable "quality" target has to be defined and a mechanism (analytical method) to achieve this target must be available. Presently, as quantifiable target and analytical method are not available, thus successful implementation of QbD is not possible. Recently suggested methods based on drug dissolution testing using the crescent shape spindle along with prediction of plasma drug levels with convolution techniques may be helpful in this regard.