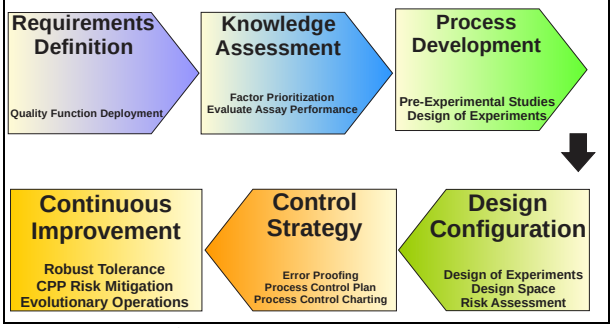
QbD (Quality by Design): A systematic approach for evaluating and improving a (production) process or marketing of statistical expertise in disguise?

Saeed A. Qureshi, Ph.D. (www.drug-dissolution-testing.com)

QbD is often promoted as an approach for improving quality, enhancing efficiencies and reducing cost of the manufacturing of pharmaceutical products such as tablets and capsules. This article provides a critical assessment of this view. It is argued that the promotion appears to be an attempt to market of the expertise in statistical analyses. This distorted view in fact appears to be causing confusion and hindrance in accepting the QbD approach. A discussion is provided highlighting the underlying issues in this regard.

QbD is a (business) process or method which may be defined as a collection of related, structured activities or tasks that produces a specific service or product for a particular user. It can often be visualized with a flowchart as a sequence of activities with interleaving decision points (see link) as shown in Figure 1.

Figure 1
Product Development Lifecycle



From: Ken Myers of Ascendant Consulting (Canada), see appendix

The concept itself is not new or complex, however, it has relatively recently been introduced in the pharmaceutical manufacturing area. Like any newly introduced concept or practice, QbD has been facing resistance and criticism for its acceptance and implementation. This article presents a view as to why there is resistance and criticism for its acceptance with the hope that if the concept of QbD is demystified and appropriately explained then its acceptance and implementation may be easier and smoother.

This write-up is a result of frustration from an intense discussion/debate on the topic on one of the LinkedIn forums (Quality-by-Design). It appears that the discussion on LinkedIn has not been about explaining the merits of QbD itself, but directed more towards marketing of consulting and advisory services of expertise of individuals which are often unrelated to development or manufacturing of pharmaceutical products and/or their qualities (see link for an example of such marketing, in particular page 10).

This article should not be considered an article on statistical analyses or scientific paper for a particular discipline, but narration of a critical view ("second opinion") or explanation of the concept. This article should particularly suit those who lack appropriate training and/or are uncomfortable with statistical analysis but would like to understand the relevancy of QbD concepts and practices in their area of expertise.

Some articles were written earlier to explain the concept and its difficulties in implementation (1, 2, 3). This time Ken Myers of Ascendant Consulting (Canada) provided a chart explaining the concept of QbD. The chart is used as a basis in describing the concept further from a scientist/chemist's perspective. With permission from Ken the chart is also attached at the end of the article.

As stated above the QbD may be defined as a collection of related, structured activities or tasks that produce a specific service or product. In this respect, the process may be broken down into six steps as shown in Figure 1.

Imagine someone tries to convince a formulation scientist/chemist using a QbD approach with the help of this chart in developing a product or method. Naturally, a reaction would be what is all this jargon about? The reason being, in the entire description there does not even once mention a word about formulation, drug, purification, method development, efficacy, adverse effect, manufacturing, or even quality which a scientist/chemist has to deal with on daily basis.

On the other hand, if this chart is presented to a production manager of a pharmaceutical manufacturing site for improving the production/manufacturing, an expected reaction would be that all of these ideas and suggestions are being used or implemented, at least to a large extent, so what is so new or different about it? Furthermore, a more disturbing response could be what is wrong with my manufacturing approach or product?

The promoter tries to explain that the QbD approach worked wonderfully well in other industries such as auto, high tech etc resulting in increased efficiency in their production and quality of the products. The response of the production manager would be, so they might have problems with their manufacturing and products, I do not! My products are of good quality, safe and efficacious and all approved by worldwide regulatory authorities. What is your problem? The next action of the production manager would be, well one can easily guess!

One may describe the situation as misunderstanding or miscommunication between the two parties, but it is more than that. From the LinkedIn discussion, one can clearly observe a hostile and abusive attitude of some of the QbD promoters for not being able to promote the concept and practice of QbD convincingly and successfully. The reason of such an attitude appears to be that promoters of QbD themselves are either not clear about the use and requirements of QbD practices or intentionally hiding or avoiding its fundamental premise. The following discussion may be considered an attempt to understand and/or decipher this confusion.

Let us consider the situation differently with an example that an analytical chemist in a research environment tries to develop an analytical method for the evaluation of bioavailability/bioequivalence of a drug product, e.g. diltiazem tablets. The chemist requires a suitable method probably based on chromatographic technique which he/she may be trained in. He/she would spend some time and most likely will develop a method which will fit his/her need. Although, the first reaction from both groups (chemist/QbD promoter) may be that QbD is not directly relevant to analytical chemistry as it is for the process (manufacturing) improvements.

However, let us change this exercise of developing the method from research laboratory to the pharmaceutical manufacturing environment, where the higher level goal is to develop a generic product of diltiazem to one that requires an analytical method for the product development/evaluation.

Although, the objective in both cases remains the same i.e. method development, however, requirements will be vastly different and much more stringent. When the method will be developed in the industrial environment, there will be a need for serious brain storming. For example, requirement of an analytical method in industry will mean, not one but probably two or more methods e.g. a method for raw material assessment (mostly pure active ingredient), method for production (active ingredient with excipients, and their degradation compounds), and then obviously one for bioavailability/bioequivalence assessment (active ingredient with possible metabolites in blood, plasma, urine or saliva etc). Therefore, clearly there is a need for three methods. There is always a possibility that one method might work but it is more likely that one would require two or more.

In the research laboratory set up, the scientist may be trained and experienced in chromatography with an available chromatograph, he/she may be comfortable using the technique. However, in the industrial environment one needs to decide the most appropriate choices based on cost and efficiencies. For example, one may use a different technique all together (e.g. MS with single ion monitoring technique) which may be much more costly initially, however, may be cost effective and efficient in the long run by developing and using only one method rather than three or more chromatographic methods. This brain storming step may be considered as planning and knowledge assessment phases as per Figure 1.

Next, one has to move to address some critical questions, e.g. how would one decide which method would be specific and robust enough. Someone has to decide about such requirements and their limits such as sensitivities, accuracy, specificity of the method and extraction procedure etc. This may be called as a process development phase.

Now the method development or experimental part starts and one has to validate the method or methods. There are standard protocols available in this regard, which require statistical analyses such as t-tests, ANOVA etc. Here, either the analyst may like to learn about the statistical principles or take the data to a statistician with a clearly defined question. For example, data (numbers) is obtained under different conditions. Does the data show or establish statistical reliability (repeatability, reproducibility) and robustness of the method? It may be argued that simple comparative statistical tests such as t-test and simple ANOVA should be done by laboratory scientists, however, more complex designs should be handled by a knowledgeable statistician with a fairly strong background about the nature of the work industry is involved in. In fact, it should be more appropriate if the statistician be consulted before the data is generated, so that he/she may help in suggesting in the required number of sets and replicates etc.

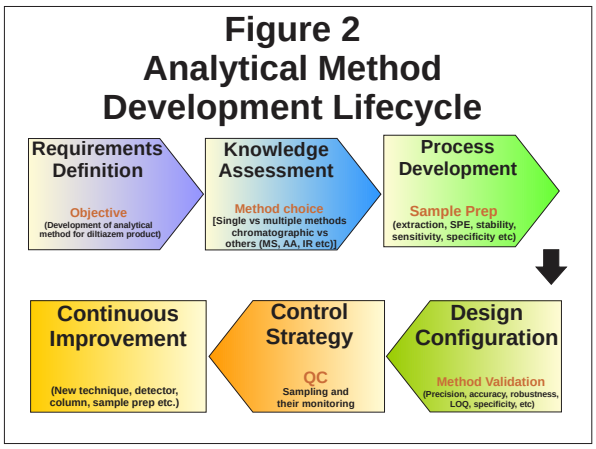
It is very important to note that there is no way around in a modern laboratory and by extension a manufacturing facility to cut short of statistics. Nobody, in particular regulatory agencies, will accept the results of any analytical method without the assessment of the robustness based on statistical evaluation.

Once the method has been developed and validated, it will then be transferred to the "shop" for use during production. In addition to the robustness, one will also require constant monitoring that the method is performing as expected during production which is a part of the control strategy. For analytical methods it is done using quality control (QC) samples. So whenever products or samples are analyzed some QC samples, having known concentrations blinded to the analyst, are added to bracket the actual samples. Accurate results of these QC samples provide assurance that method was working as expected.

Further, as a part of good project management, one must keep an eye on the future as well for increasing the efficiencies and reducing the cost of the method. This may be achieved by simplifying the existing method or adopting different methods, which could be simpler, faster, cheaper, or more reliable/robust. For example, the availability of very small particle size chromatographic phases or shorter columns with extremely high efficiency separation which may eliminate having different chromatographic methods. This should become a continuous improvement strategy.

Now let us see if one can fit this systematic approach/strategy of analytical method development in the QbD format (Figure 2). Looking at Figure 2, it appears certainly one can use or adopt QbD approach for analytical method development. The important thing here is to note that this strategy is suggested by an analytical chemist with some knowledge of QbD concept. Although, as stated earlier that it may be assumed that QbD approach is for production or processes, however, as described here one may also apply the QbD principle in the analytical laboratory as well, in fact one should. Another important thing to note is that there is nothing new here, more or less all analytical laboratories/facilities have been using this type of approaches for years without naming it as QbD.

It is to be noted that in addition to requirements of expertise of analytical chemistry, at least some knowledge of statistics is required as well, as method validation steps requires significant use of statistical analyses.



Let us now move from development of an analytical method to a manufacturing/production set up. Description is based on the development and production of a generic product, e.g. diltiazem, where an innovator's or branded product is available on the market.

Obviously, first of all one has to set a clear objective of the project/process which is to manufacture a drug product bio-equivalent to the branded product reflected by similar human drug blood level characteristics.

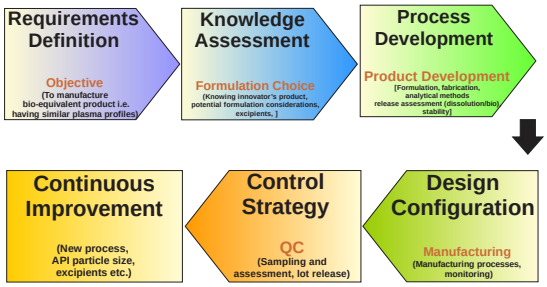
The next step will be a brain storming session or knowledge assessment. One could discuss all kinds of possible information about the current knowledge concerning the branded product, physical (solubility, particle size, stability) and pharmacokinetics characteristics of API, its stability, degradations, potential interaction with excipients etc., availability or development of analytical methods (chromatographic, dissolution etc.)

The next step would be process development i.e. formulation development, its testing for release characteristics (dissolution), and then human bioavailability/bioequivalence study. Strategies and consideration for repeats if and when required. Developing manufacturing conditions and scale up etc.

Once the process is developed then the whole thing should be transferred to the manufacturing floor, with its own check and balances.

Control strategy means monitoring and ensuring that all processes are within limits and keeping a record of end of the line sampling and checking the final product and release with final specifications.

Figure 3
A Generic Product Development Lifecycle



These steps are described in Figure 3. The chart is simple but global in nature. Each bullet (sub-topic) in the process may represent one or more sub systematic approaches, just like one described for the development of the analytical method earlier. It is possible that this description of QbD for manufacturing may have "holes" or "errors" which may be laughed at. Certainly, that is the point, while describing or developing this chart I was not sure or confident enough as with the previous one (analytical chemistry). The reason being that by training I am a scientist/chemist, thus have expertise and an understanding of the topic (analytical chemistry) hence was much more confident in developing a systematic approach for the discipline. On the other hand, I have some awareness about the manufacturing of generic products, but not enough, to provide myself with sufficient confidence for describing the strategy to the full extent. Point being, for developing a systematic approach (aka QbD), one must have extensive and intimate knowledge and experience of the specific manufacturing type. The experience of manufacturing in general may be useful but not sufficient for developing and implementing strategy such as QbD for pharmaceutical manufacturing.

This is perhaps one of the biggest weakness and fallacy of the promoters of QbD that they present/impose QbD practices on people/industry for which they may or may not have intimate or extensive knowledge and/or experience. It is important to note that approaches or practices which may have worked in some industries or environments may not be workable in other industries and in fact may not even be required for other industries. A more suited approach should be that the concepts or strategy be described to people in different industries and then it should be left up to them to determine/decide how will they develop the QbD strategy and design for their specific purpose. Point being, authors or implementers of the of the QbD plan for manufacturing of a generic product must be those who have expertise and hands-on experience with the science of formulation and manufacturing of drugs (not from auto or the high tech industry) and not from those having a specific expertise such as statistics and/or business administration only. Otherwise, suggestions and recommendation would be such that they can be counterproductive as it appears to be the case at present.

Let us now consider what promoters of QbD are "bringing to the table". Their main argument is that the pharmaceutical industry is not very efficient in producing cost effective and quality products. The reason often provided is that the industry is not following QbD principles, thus such deficiencies. Their argument is often based on a view that other industries follow the QbD principles thus producing cost effective and quality products.

It is interesting to note that people:

1. Who have limited and/or recent experience in the pharmaceutical industry;
2. Have limited experience with the various scientific disciplines involved, in particular formulation development, pharmaceutics etc;
3. Might have had used occasionally few medicines on the recommendations of others (e.g. physicians);
4. And hardly would have any ideas in assessing the effectiveness of medicines by themselves;

Would blame the industry as a whole in one shot, claiming that it does not know what it is manufacturing. How reliable and relevant can this argument be?

It is very similar to when people, all of sudden start writing articles about bad quality of food served in restaurants. That is, the food is awful and restaurants are not serving the clients' needs, thus industry is not caring about the health of their customers. On the hand, restaurants are operating as usual and people are enjoying the food. Obviously, people will start seeking the motives behind the write-ups or claims.

Here the motives of food critics may be noble but do not appear reliable and relevant. It may be argued that they (food critics) may like to see description of the quality and cost effectiveness in certain quantitative format ***which may promote their own expertise as well***. The following elaborates on this argument:

Let us restrict the analogy of restaurants to one specific restaurant. There is an impression that the food quality as measured by the taste or "customer satisfaction" is not as good as it used to be. How should one decide about the truth of this perception? The only way to get a quantitative answer to this question is to conduct a survey of clients' opinions and analyze the results using statistical methods. Simple survey results without statistical analysis will still be considered as qualitative and the outcome by chance. The assessment of the quality aspect requires statistical analysis to get a reliable opinion (removing the chance factor).

With the statistical analysis, one will be able to ascertain whether the food is indeed bad or good (i.e. perception was incorrect). Obviously, if the food/taste was bad then something has to be changed. Once the change is made, or during the process of change (trying multiple ingredients or cooking styles), once again one will require statistical analysis to ascertain that change, and which change, has been effective. The same thing will happen if someone tries to improve the quality of "good" food, again a statistical design and assessment will be required. This systematic approach of development, improvement and evaluation of products ("food") based on statistical design and analysis is considered QbD approach. It is obvious that QbD requires an extensive use and expertise of statistical design and analyses.

Similarly promoters of QbD in pharmaceutical industry, like food critics, are in fact promoters of the use of statistics for the assessment of the quality. The use of statistics by itself is not bad, in fact, is required and as stated above is a must. However, it is not clear why the promoters of QbD do not highlight this reality and usefulness of statistical analyses, but promotes the concept of QbD with all kinds of examples and analogies, often unrelated, but statistics. This creates doubt about their motives and also hindrance for the acceptances and implementations of the QbD approach.

Before moving further, let us consider a very basic overview of statistics needed in this regard. At its heart, the use of statistics is to compare two numbers/outcomes accepted/expected vs. obtained. As in life nothing is absolute, both of these numbers (accepted or obtained) will differ (i.e. variability or standard deviation) from batch to batch (i.e. sample to sample) as well as within each group of values (accepted vs. obtained). However, results or data usually follow a set pattern (i.e. distribution e.g. normal, uniform etc.). There is a mathematical approach, known as statistics, which can be used to establish, using means and variability of accepted or observed values, as to whether they are from the same or different patterns (distributions) i.e. perception is true or false. This mathematical or statistical approach provides quantitative and unbiased answers for decision making or makers. The statistical designs are used to analyze appropriately and accurately, seeking answers for perceptions at every stage of manufacturing. QbD promotes this statistical approach in a systematic way based on data analyses for evaluating impact of critical components/steps of the manufacturing such as purity of APIs, analytical method development, bio- or clinical studies, and then characteristics of the end products.

The lead references in prompting this systematic (statistical or QbD) approach for manufacturing are of J.M. Juran and W.E. Deming Both gained their successes and fames with their expertise in statistical analyses and their application in quality improvement and management. Furthermore, in this regard, a term often used is *Six Sigma*, which seeks to improve the quality of process outputs by identifying and removing the causes of defects (***errors***) and minimizing ***variability*** in manufacturing and business processes based on ***statistical modeling*** of manufacturing processes (e.g. see link).

It should, therefore, be very clear that QbD is a quantitative approach based on statistical analysis for measuring the quality of a process, product, analytical method etc. It is a discipline of statistics applied to manufacturing either collectively or individually to different components of manufacturing. Although, the statistics discipline may be learned like any other subject, however, having a knowledgeable statistician, or team, on board is perhaps a better idea. The job of the statistician or team is to provide answers in a quantitative fashion on the perceptions, which should lead to a smoother decision making process for others such as formulators, production managers, chemists etc.

It may be worth repeating that QbD is a systematic approach for quantitative measurement of perceptions of quality or efficiencies based on the statistical analysis

used for, just like any other tool, eventually improving quality of products or improved manufacturing.

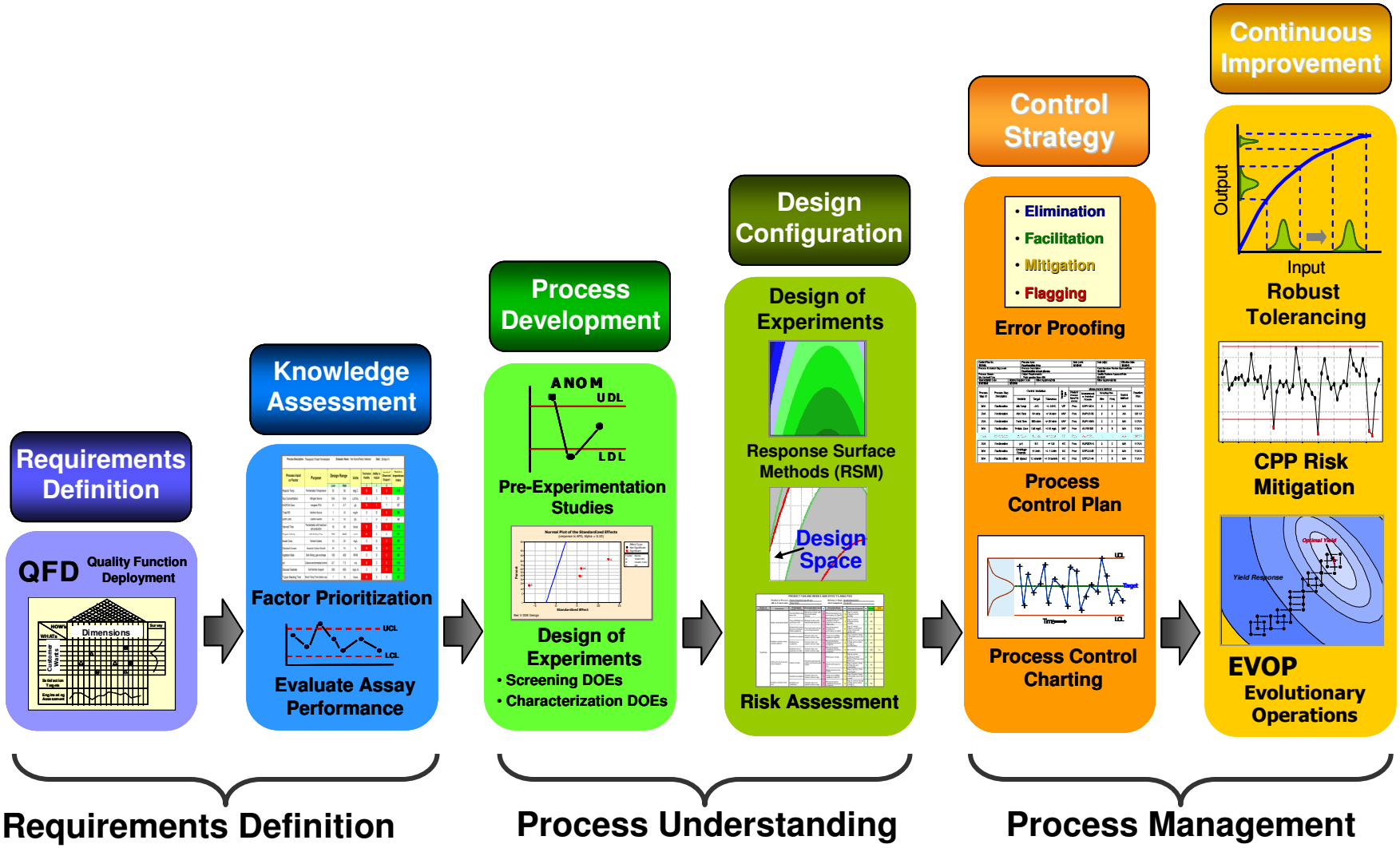
It appears that promoters of QbD have confused the situation which in fact may be hindering for its implementation. The following may be considered as some examples which are causing the confusions and require attention and clarifications:

1. The claim that the pharmaceutical industry is not efficient and not producing cost effective products is a ***promoted perception*** until supported by a quantitative answer based on statistical analysis (aka QbD).
2. Consideration should be given in describing that ***the practice of QbD is an approach of statistical analyses using valid statistical design***, which may help production managers/operators in making appropriate decisions about improving the quality and efficiency of the manufacturing.
3. Often it is claimed that QbD is much more than statistical analyses. If that is the case, then it should be clearly described "***what is much more***" in some measureable and quantifiable manner. What extra discipline or expertise is this referred to and how can it be acquired?
4. Why would not ***a production manager with knowledge of statistics be more appropriate in implementing QbD***? It appears that experience and expertise of a production manager may be described as a "what is much more" part of the QbD.
5. Terminologies such as CPA (Critical Product Attributes), CPP (Critical Process Profiles), RTRT (Real Time Release Testing), Design Spaces (DS), and others, commonly used are confusing and appear as ***a foreign language***. These appear borrowed from a manufacturing aspect, when the manufacturing aspect includes so many other process (e.g. analytical method development, bioequivalence assessment, regulatory assessment). These terminologies need to be translated into more relevant descriptions. This is similar to providing services to customers in their language rather than having customers being expected to learn the vendors' language.
6. Why does the ***initiation and implementation of QbD require support of regulatory bodies***? Why are such bodies considered more appropriate for developing QbD guidelines for ***developing and/or manufacturing of products***?
7. The successful application of QbD principles ***require a clear definition of quality which has to be agreed upon***. For example, in this respect, what defines "quality" of a pharmaceutical product, such as a tablet/capsule product?

In conclusion, it may be stated that QbD may be considered as a systematic approach for manufacturing emphasizing the use of statistical design and analyses tools. Promotion of QbD approach should clearly highlight this reality, which will help in its acceptance in the industry. The production managers should gain more awareness of this approach along with underlying statistical principles to effectively apply QbD in the operations of the plants and productions of the products.

Appendix

Product Development Lifecycle



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