QBD- A CHALLENGE TO THE PHARMA INDUSTRY

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Abstract

QbD is a best solution to build a quality in all pharmaceutical products but it is also a major challenge to the Pharmaceutical industry whose processes are fixed in time, despite inherent process and material variability. Under this concept of QbD throughout designing and development of a product, it is essential to define desire product performance profile [Target product Profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA). On the basis of this we can design the product formulation and process to meet the product attributes. This leads to recognize the impact of raw materials [critical material attributes (CMA)], critical process parameters (CPP) on the CQAs and identification and control sources of variability. QbD is an emerging idea which offers pharmaceutical manufacturer with increased self-regulated flexibility while maintaining tight quality standards and real time release of the drug product.

Key words: Quality by Design (QbD), Target Product Profile (TPP), Target Product Quality Profile (TPQP), Critical Quality Attributes (CQA), Critical Material Attributes (CMA), Critical Process Parameter (CPP).

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INTRODUCTION

The Food and Drug Administration (FDA) [1-3] and pharmaceutical industry [4-6] are talking about quality by design, and there are many important terms that are used as part of this discussion. However, industry comments indicate that there is still much confusion in the generic industry as to the meaning of quality by design and its associated nomenclature.

In order to describe quality by design, we must first define what we mean by quality. Quality is acceptably low risk of failing to achieve the desired clinical attributes. Janet Woodcock (Director for the Center for Drug Evaluation and Research) defined pharmaceutical quality as a product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer [1]. The following equation indicates where quality comes from:

\[
\text{Pharmaceutical Quality} = f(\text{drug substance, excipients, manufacturing, packaging}).
\]

In order for quality to increase, it must be built into the product. To do this requires understanding how formulation and manufacturing process variables influence product quality; this is the function \( f \) in the equation above.

Quality by design (QbD) encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. In 2002, the FDA announced a new initiative (cGMP for the 21st Century: A Risk based Approach) [7]. This initiative intended to modernize the FDAs regulation of pharmaceutical quality, and establish a new regulatory framework focused on QbD, risk management, and quality system. The initiative challenged industry to look beyond quality by testing (QbT) for ensuring product quality and performance. An important part of QbD is to understand how process and formulation parameters affect the product characteristics and subsequent optimization of these parameters should be identified in order to monitor these parameters online in the production process. Thus, QbD is a holistic approach where product specifications, manufacturing process and critical parameters are included in order to ease the final approval and ongoing quality control of new drug. As stated in recent guidance from FDA, QbD is a systematic approach to development that begins with predefined objectives, and emphasizes product and process understanding and process control, based on sound science and quality risk management. QbD requires an understanding of how product and process variables influence product quality. In addition to this new concept being considered by FDA in its cGMP initiative, two important guidance documents were

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published as part of International Conference on Harmonization (ICH) guidelines: Q8 Pharmaceutical Development and Q9 Quality Risk Management. The former describes the expectations for the pharmaceutical development section of the Common Technical Document (CTD); the latter presents approaches to producing quality pharmaceutical products using current scientific and risk based approaches. Q10 Pharmaceutical Quality System also describes model for an effective quality management system for pharmaceutical industry. The application of QbD principles to pharmaceutical development and manufacturing has gained a lot of interest in the literature recently. The article describes a systematic and general scheme to implement QbD in the pharmaceutical industry and also illustrate key aspect of QbD process in the pharmaceuticals.

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Current state</th>
<th>Desired QbD state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical development</td>
<td>Empirical; typically univariate experiments</td>
<td>Systematic; multivariate experiments</td>
</tr>
<tr>
<td>Manufacturing process</td>
<td>Locked down; validation on three batches; focus on reproducibility</td>
<td>Adjustable within design space; continuous verification within design space; focus on control strategy</td>
</tr>
<tr>
<td>Process control</td>
<td>In-process testing for go/no-go; offline analysis</td>
<td>PAT utilized for feedback and feed forward in real time</td>
</tr>
<tr>
<td>Product specification</td>
<td>Primary means of quality control; based on batch data</td>
<td>Part of overall quality control strategy; based on product performance</td>
</tr>
<tr>
<td>Control strategy</td>
<td>Mainly by intermediate and end product testing</td>
<td>Risk-based; controls shifted upstream; real-time release</td>
</tr>
<tr>
<td>Lifecycle management</td>
<td>Reactive to problems and OOS; post approval changes Needed.</td>
<td>Continual improvement enabled within design space</td>
</tr>
</tbody>
</table>

Table 1. Comparison of the current state to the future desired QbD state.

WHY QbD? [8]

Pharmaceutical QbD is a systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding based on sound science and quality risk management (ICH Q8R2).

Quality by design helps for

- Higher level of assurance of product quality.
Cost saving and efficiency for industry and regulators.
Facilitate innovation
Increase manufacturing efficiency.
Reduce product rejects.
Minimize and eliminate potential compliance action.
Enhance opportunities for first cycle approval.
Streamline post approval changes and regulatory processes.

**Process Understanding: [9]**

Process understanding is the major goal of a QbD program. A complete list of characteristics of a successful QbD program is summarized in Table 1.2.

A process is well understood when

- All the critical sources of variability are identified and explained;
- Variability is managed by the process, and;
- Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions

| ✓ product design and process development |
| ✓ Risk-based, science based |
| ✓ Primary focus is patient safety and product efficacy |
| ✓ Business benefits are also drivers |
| ✓ Results in improved process understanding |
| ✓ Results in improved process capability/robustness |
| ✓ Systematic development |
| ✓ Holistic – applies to all aspects of development |
| ✓ Multivariate – interactions are modelled |
| ✓ Provides PAR, design space, or suitable equivalent |
| ✓ Requires a significant reduction in regulatory oversight post approval |

**Table 2. Characteristics of a successful QbD program involves**
Figure1: Key steps in implementation of QbD for a Pharmaceutical product

Defining Product Design Requirements And Critical Quality Attributes:

In order to design quality into a product, the requirements for the product design and performance must be well understood in the early design phase. In pharmaceuticals, these product requirements can be found in a Quality Target Product Profile (QTPP). In addition to defining the requirements to design the product, the QTPP will help identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties. In some cases, these attributes are directly measurable, for example, potency. In other cases, surrogate measurements are developed indirectly to measure the quality or performance, for example, in vitro dissolution for a controlled release product.

Identifying Quality Target Product Profile (QTPP)

The target product profile (TPP) has been defined as a “prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized” [10]. This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g., sterility and purity) appropriate for the intended marketed product [11]. The concept of TPP in this form and its application is novel in the QbD paradigm. The Quality Target Product Profile (QTPP) is a term that is a natural
extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The QTPP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. QTPP is related to identity, assay, dosage form, purity, stability in the label [12].

Identifying CQAs

Once TPP has been identified, the next step is to identify the relevant CQAs. A CQA has been defined as “a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality” [13]. Identification of CQAs is done through risk assessment as per the ICH guidance Q9 (Figure.1). Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments. Such knowledge may also include relevant data from similar molecules and data from literature references. Taken together, this information provides a rationale for relating the CQA to product safety and efficacy. The outcome of the risk assessment would be a list of CQAs ranked in order of importance. Use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm.

![Diagram showing the relationship between QTPP and TPP within the QbD paradigm]

Figure 2: An illustration of how under qbd the identification of critical process parameters and critical material attributes is linked to the qtpp and finally to tpp that represents the clinical safety and efficacy.
Critical Process Parameters

What is a Process Parameter?

There is confusion about what is a process parameter. Previously, some have defined a critical process parameter (CPP) as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency.

We propose that process parameter be understood as referring to the input operating parameters (mixing speed, flow rate) and process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. For example, a material attribute, such as moisture content, should have the same target value in the pilot and commercial processes. An operating parameter, such as air flow rate, would be expected to change as the process scale changes.

For a given unit operation, there are four categories of parameters and attributes

- Input material attributes
- Output Material attributes
- Input operating parameters
- Output process state conditions.

What is an Unclassified Process Parameter?

We recognize that there are many material attributes and process parameters that are important and even essential to product quality, but it is of little value to define all parameters as critical. Thus we propose three categories for attributes or parameters: unclassified, critical, or non-critical. The criticality of an unclassified parameter is undetermined or unknown. Sponsors’ pharmaceutical development studies can provide the additional data needed to classify an unclassified parameter as critical or non-critical. For a process or dosage form we expect wide agreement on the set of attributes or parameters that need classification. Prior experience and standard texts will guide this process.
These UPP may later be classified as critical or non-critical. For example, in the granulation process, the impeller speed should clearly be identified as an unclassified process parameter because if impeller speed were zero the process step would not be successful. However, this does not mean that impeller speed is always a critical parameter. If development studies demonstrated the granulation was not affected by realistic changes in impeller speed, it would not be identified as critical. An application that did not include the results of pharmaceutical development studies investigating the criticality of the UPP would have a large number of UPP remaining in the final submission.

**What is a Critical Process Parameter?**

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. A simple example is that an impeller speed of zero will always fail. Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest to the sponsor for each process parameter. The POS can also be considered as the extent of the sponsor’s quality system with respect to these parameters. This definition is at the discretion of the application that sponsor must balance the trade-offs in its definition. The POS defines the scope of the application and the sponsor’s quality system so that going outside of the POS must need an amendment or supplement to the application. Thus sponsors benefit from defining a large feasible POS. The cost of a large POS is the need for the pharmaceutical development (in the form of prior knowledge, process models or experimental data) to cover the POS and the increased chance that a parameter will be found critical in the large POS. The only constraint on the narrowness of the POS is that the POS must encompass the variability of the process parameters around their target values.

Our criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range (PAR)(see explanatory footnote on first page of article), which is the range of experimental observations that lead to acceptable quality. A sponsor has the option of conducting experimental observations over the entire POS; in this case the POS could be equivalent to the PAR. Alternatively a sponsor may use prior knowledge, mechanistic models and trends from the PAR to draw conclusions about sensitivity over a POS that is larger than the PAR. If the lack of interaction part of the test cannot be met, then the parameter remains a UPP. A parameter is critical when there is
an observation of failure or a trend to failure predicted within the POS. If the interaction between two parameters is significant enough to predict a potential failure in the POS, then both parameters should be considered as critical.

The most definitive way to identify critical and non-critical parameters is by scientific investigations involving controlled variations of the parameters. The focus in the process development report is on the additional studies that build this knowledge. These studies can be conducted on pilot or lab scale and do not need to be conducted under current Good Manufacturing Practice. When the sensitivity of process parameters is established, this can be used to design appropriate control strategies.

However, it may not be possible (due to economic and time constraints) to conduct scientific investigations on all UPP. We believe that prior knowledge and experience with the unit operations can be used to classify some UPP. The prior knowledge can be used in a formal risk assessment process to prioritize unclassified parameters for further experimental study. This is potentially a challenging issue for FDA review, if the reviewer does not agree with the risk assessment used to classify parameters as non-critical, then all further conclusions may be in doubt because a potential critical variable was left out of the experimentation that was used to develop a design space.

Our criteria for identifying critical and non-critical process parameters are based on the sensitivity of product characteristics to changes in the process parameters. Other approaches presented in the literature link the classification as critical to the variability in a process parameter. [14, 15]

**Uniqueness of Critical Process Parameters**

Because of the broadness of the CPP definition it is possible for two investigators to examine the same process and come to a different set of CPP. The set of CPP is not unique, but the chosen set must be sufficient to ensure product quality.

Different sets of CPP can have several origins. One is that the definition of operating parameters depends on the engineering systems installed on a piece of process equipment. For example, one fluid bed dryer may define the product temperature as an operating parameter and have an internal control system (a thermostat) that maintains that temperature, while another fluid bed dryer may have inlet air flow rate and inlet air temperature indicated as operating parameters. The batch record for the first unit might indicate a fixed temperature, while the second unit would have a design space that indicated the
A combination of inlet air flow rate and inlet air temperature that would insure the appropriate product temperature.

Another source of differences in the set of CPP comes from the balance between control of operating parameters and material attributes. Morris [16] indicates that set of CPP and CMA (which he refers to as process critical control points (PCCP)) can affect the scale up process.

- PCCPs are preserved throughout scale-up, the magnitude of the responses may not scale directly, but the variables being monitored reflect the “state” of the process
- Monitoring material properties makes scaling less equipment dependent (as opposed to only monitoring equipment properties) equipment differences (scale and type) may have an effect, however, differences in the material should reflect significant changes in the PCCPs

<table>
<thead>
<tr>
<th>Parameter type</th>
<th>Definition</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non critical process parameters</td>
<td>Not critical</td>
<td>• No failure in target product quality profile observed or predicted in the potential operating space (POS) and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No interactions with other parameters in the proven acceptable range (PAR)</td>
</tr>
<tr>
<td>Unclassified process parameters (UPP)</td>
<td>Criticality unknown</td>
<td>• Not established</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The default in the absence of pharmaceutical development</td>
</tr>
<tr>
<td>Critical process parameter (CPP)</td>
<td>Critical (control needed to ensure quality)</td>
<td>• Failure in target product quality profile (TPQP) observed or predicted in the potential operating space (POS), or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Interactions with other parameters in the proven acceptable range</td>
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Table 3: Classification of process parameters

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Pharmaceutical unit operation</th>
<th>Critical process parameters</th>
<th>Potential quality attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Roll Compaction</td>
<td>Roll Speed, Gap Setting, Roll Pressure, Oscillation Degree / Speed, Screen Size Screen Type, Feed Rate if separate mill</td>
<td>Appearance, Ribbon/Particle Size and shape, Ribbon density, strength, Thickness, Granule Porosity</td>
</tr>
<tr>
<td></td>
<td>Wet Granulation</td>
<td>High Shear Granulation</td>
<td>Fluid Bed Granulation</td>
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<td>------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry mix time, Impeller speed, configuration and location, Chopper speed and configuration, and location, Spray nozzle type and location, Method of binder addition, Binder Fluid temperature, Binder addition rate and time, Post granulation mix time, Bowel temperature.</td>
<td>Mixing Time, Spray Nozzle (Type/configuration/pattern), Binder fluid temperature, Binder fluid addition rate and time, Inlet air flow, vol., temperature, dew point, Product temperature, Exhaust air temperature and flow, Filter properties and size, Shaking interval.</td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drying</td>
<td>Fluid Bed Drying</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Inlet air flow, vol., temperature, dew point</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Product temperature, Exhaust air temperature and flow, Filter properties and size, Shaking interval, Total drying time.</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Tray Drying</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quantity of carts and trays per chamber, Quantity of product per tray, Drying time and temperature, Air flow, Inlet Dew Point.</td>
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<tr>
<td></td>
<td></td>
<td>Vacuum/Microwave</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jacket Temperature, Condenser temperature, Impeller Speed, Vacuum strength, Microwave potency, Electric field Energy Supplied, Product Temperature.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Milling</td>
<td>Impact/Cutting/Screening Mills</td>
<td>Mill Type, Speed, Blade Configuration and type, Screen size and type, Feeding rate.</td>
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<td></td>
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</table>
Control Strategy

Control strategy is defined as “a planned set of controls, derived from current product and process understanding that assures process performance and product quality” [17]. The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements: procedural controls, in process controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach.
A control strategy may include input material controls, process controls and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production.

Every process has a control strategy right now. Figure 6.1 shows a simplified quality assurance diagram under the current regulatory evaluation system. In this system, product quality is ensured by fixing the process to produce the active ingredient, raw material testing, performing the drug product manufacturing process as described in a fixed batch record, in-process material testing, and end product testing.

![Figure 6.1: A Simplified Quality Assurance Diagram](image)

The quality of raw materials including drug substance and excipients is monitored by testing. If they meet specifications or other standards such as USP for drug substance or excipients, they can be used for manufacturing of the products. As the drug substance specification alone may not be sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. Potentially significant changes to the drug substance manufacturing process will require the drug product manufacturer to file supplements with the FDA.

The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in-process tests, such as blend uniformity or tablet hardness. Manufacturer are also not permitted to make changes to the operating parameters (a
large number of UPPs) specified in the batch record or other process changes without filling supplements with the FDA.

This combination of fixed (and thus inflexible) manufacturing steps and extensive testing is what ensures quality under the current system. A combination of limited characterization of variability (only three pilot lots for innovator products and one pilot lot for generic products), a failure of manufactures to classify process parameters as critical or non-critical, and cautiousness on the part of regulator leads to conservative specifications. Significant industry and FDA resources are being spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. The rigidity of the current system is required because manufacturers may not understand how drug substance, excipients, and manufacturing process parameters affect the quality of their product or they do not share this information with FDA chemistry, manufacturing and controls (CMC) reviewers. Thus the FDA CMC reviewers must act conservatively.

Pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables to assure the quality of the finished product. The end product testing only confirms the quality of the product. In this example, PAT provides tools for realizing the real time release of the finished product although its use is not required under the paradigm of the Quality by Design.

Figure 4: An Example of Control Strategy for QbD Process
Implications of Process Parameter Classification

The classification of process parameters as critical or non-critical is essential to evolve the control strategy toward the QbD based goal. Full classification of all parameters as either non-critical or critical can lead to reduced end-product testing. It is the uncertainty about the UPP that leads to extensive testing.

Without development studies, UPP may need to be constrained at fixed values or narrow ranges (used to produce acceptable exhibit batches) because they might be critical. The presence of UPP also leads to inclusion of extensive release and in-process tests into the control strategies. The goal of development studies is to move parameter from unclassified (criticality unknown) to either non-critical or critical. This classification is an important step toward a flexible manufacturing process because unclassified parameters classified as non-critical may be monitored and controlled via monovariant ranges or as part of a sponsor’s quality system (see Table II). For non-critical parameters it may be possible to designate a normal operation range (NOR) up to (or beyond) the proven acceptable range (PAR) depending on trends and prior knowledge. The superposition of NOR for non-critical parameters would be considered as part of the design space.

<table>
<thead>
<tr>
<th>PARAMETER TYPE</th>
<th>POTENTIAL CONTROL STRATEGIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-critical process parameter(non-CPP)</td>
<td>Univariant range in batch record Under control of sponsors quality system</td>
</tr>
<tr>
<td>Unclassified process parameter(UPP)</td>
<td>Extensive release testing because of uncertainty. Fix at exhibit batch value or narrow range to ensure no interactions.</td>
</tr>
<tr>
<td>Critical process parameter (CPP)</td>
<td>Reduced release testing when all critical process parameters are identified, monitored and controlled. Proven acceptable range if no evidence of multivariate interactions Design space to allow multivariate changes. Feed back control based on measurement of material attributes.</td>
</tr>
</tbody>
</table>

Table 5: Impact of Classification of Process Parameters on Control Strategy
The ranges of critical parameters must be constrained to a multidimensional design space or fixed at values of all parameters known to be acceptable. Univariate PAR can be used for critical parameters only when there is evidence that there are no significant interactions between the CPP. However, the establishment of this knowledge about CPPs may render them lower risk than UPP. A control strategy appropriate to the known CPP may also have less need for release testing than one for a process with many UPPs.

**Design Space**

In the presence of interacting critical process parameters a design space is one approach to ensure product quality although it is not a check-box requirement. The current definition of design space is “The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” [13] This definition evolved from early ICH Q8 drafts where design space was defined as “the established range of process parameters that has been demonstrated to provide assurance of quality” [18]. The change emphasizes the multidimensional interaction of input variables and closely binds the establishment of a design space to a conduct of a DOE that includes interactions among the input variables. A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process.

Submission of a design space to FDA is a pathway obtaining the ability to operate within that design space without further regulatory approval. A design space is a way to represent the process understanding that has been established. The benefits of having a design space are clear; one challenge to the effective use of a design space is the cost of establishing it.

In a typical design space approach a sponsor identifies the unclassified parameters and then does a DOE on some of the unclassified parameters with the other unclassified parameters fixed. Thus the end is a regulatory situation where there is some space for the selected parameters but no flexibility for the other parameters. This operating parameter based design space is limited to the equipment used to develop the design space. It might change on scale up or equipment changes.

In the development of a design space, the key issue to efficiency is demonstrating or establishing that the unclassified parameters left out of the DOE are truly non-critical process parameters and are thus by our definition non-interacting. Before attempting to establish a design space, effort should be...
invested to reduce the number of unclassified process parameters. This may involve a screening DOE to rule out significant interactions between process parameters. When they are non-interacting, univariate ranges for non-critical parameters are appropriate and can be added to the design space presentation without additional studies.

It is best to exploit the non-uniqueness of CPPs to define the design space in terms of scale independent (dimensionless) parameters and material attributes. Understanding the design space in terms of material attributes allows scale up and equipment changes to be linked to previous experiments. The scalability of the design space can be evaluated in the transfer from lab to exhibit batch manufacturing.

**Figure 5: Illustration of design space**

**Figure 6: Road map of quality**

**Feedback Control and PAT**

Application of PAT [9] may be part of a control strategy. ICH Q8(R) [11] identifies one use of PAT as ensuring that the process remains within an established design space. In a passive process, PAT tools provide continuous monitoring of CPP to demonstrate that a process is maintained in the design space.
In process testing of CMA can also be conducted online or in line with PAT tools. Both of these applications of PAT are more efficient ways to detect failures. In a more robust process, PAT can enable active control of CPP, and if there is variation in the environment or input materials the operating parameters can be adjusted to keep the CMA under control to ensure quality.

A PAT system that combines continuous monitoring of CMA (instead of CPP) can potentially be combined with feedback control of process parameters to provide an alternative to design space based control strategies. A problem with design space is that it can limit flexibility. A design space is usually a specified space of process parameters that has been demonstrated to provide acceptable quality. There may be sets of process parameters that lead to acceptable quality but were not explored in the establishment of the design space. Thus, pursuit of a design space can be movement in the opposite direction from a flexible and robust manufacturing process. Direct assessment of product quality via PAT may support more flexibility and robustness than is represented by the design space. When CMA can be actively monitored and feedback control applied to the CPP, then variation in the environment or input materials can be counteracted by new values of the CPP (even values outside of a design space that represents prior experience) to keep the CMA within desired limits. When direct assessment of product quality by PAT is established, it may be more valuable to invest pharmaceutical development resources toward an active control system than toward documentation of a design space.

**SUMMARY:**

Quality by design is an essential part of the modern approach to pharmaceutical quality. This paper clarifies the use of QbD for ANDAs including:

- Emphasis on the importance of the Target Product Quality Profile in articulating a quantitative performance target for QbD.
- Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process.
- Clarification that critical process parameters are operating parameters and should be combined with critical material attributes to describe the relation between unit operation inputs and outputs.
- A definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes.
The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice

An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs.

CONCLUSION:

Quality by Design (QbD) is unquestionably ready to help an organization solve the perennial challenges of drug development and manufacturing. The readiness of any organization for QbD begins with an understanding of QbD basics, benefits, and barriers to implementation, followed by a readiness assessment that can ensure that one has the right mindset, priorities, and resources aligned for a successful implementation. As long ago as 2004, Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research, stated that the basic principles of QbD are almost diametrically opposed to established industry practices. By increasing scientific understanding of products and processes, QbD makes risk-based compliance possible. Its goal is not to eradicate variability in processes but to develop a process that can accommodate the range of acceptable variability for maintaining product quality. Starting from a Target Product Profile (TPP) based on Critical-to-Quality Attributes (CQA) (Fig.2), one can then use appropriate analytical methods and tools to understand Design Space.

Such methods and tools include high-end statistics like multivariate analysis, modelling tools, and design of experiments (DoE). They are used to help understand the most critical process parameters (CPPs) and map out the Design Space so that one can create an in-control operating space, preferably near the center of the Design Space where the most process robustness will be found. And
with a demonstrable, scientific understanding of Design Space, process can be continuously improved without additional regulatory review.

Robust, scientifically understood processes that allow for variation without compromising quality generate operating improvements that translate into business benefits, including: Faster time to market and reliable supply, Fewer lost batches, Fewer manufacturing deviations, Reduced out-of-specification results, reducing rework, Reduced compliance exposure and increased regulatory flexibility with fewer remediation and the ability to make process changes without re-filing. These operating successes also help reinforce a “right-first-time” culture, where quality means continuously creating more value, not simply correcting problems.

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