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Quality by Design: Working with your Contract Manufacturer

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Abstract An effective Quality by Design program executed with a Contract Organization is based on open communication to ensure complete knowledge transfer and risk assessment. Evaluating and addressing gaps early in the product lifecycle can ensure robust processes are developed leading to successful commercialization of a dosage form meeting quality target product profile requirements. Sponsor concerns over cost, timeline, and sharing of proprietary information can sometimes derail the Quality by Design process, leading to delays and unnecessary repetition of experimentation late in the development process. Current regulatory environment not only encourages but mandates complete information sharing between contractor and sponsor to facilitate the development and commercialization of quality products using sound QbD principles.

Quality by Design (QbD) is based on sound scientific principles and quality risk management to ensure that the aspects of quality are incorporated into the design of the process and that the process consistently meets safety and efficacy targets. Even though the benefits of QbD are obvious, a Contract Development and Manufacturing Organization (CDMO) in the pharma industry often faces challenges in executing QbD programs due to the sponsor's pre-determined expectations of product development requirements in terms of scope and key milestones/timelines. A contract manufacturing organization must maximize efficiency during transfer and process development to gain the knowledge necessary to design quality manufacturing processes and still meet timelines and budget.

Often times the sponsor focus is on determining a set of target operating conditions that meet initial primary quality targets, so as to quickly progress to clinical trial manufacturing and product commercialization. What is initially believed by the sponsor to be a cost effective and streamlined approach to product development can result in redundant or ineffective studies. Characterization trials must be repeated to truly understand the process. Without sufficient up front work, and time being dedicated to fully understanding the relationship of product critical quality attributes (CQA's) and critical process parameters (CPP's), the risk is high that unexpected excursions outside of acceptable ranges prior to validation will occur. Costly delays in commercialization, or worse yet, post commercial shifts in materials, process, or equipment performance will lead to a commercial product with numerous deviations and a visibly poor quality track record.
Implementing an organized and effective QbD plan for product development with a sponsor requires mutual agreement on the strategy and integrating execution targets into key milestones and timelines. The resulting outcome is a road map for the development of the product from the very beginning. Another significant challenge from a CDMO's perspective is that they don't always see the project from the "beginning" (Pre-formulation and Phase 1), and the sponsor project can instead come in the form of a technical transfer of a formula and/or process that perhaps wasn't developed using QbD principles. Often the process design space is not well understood and sponsor concerns of making "process changes" within the clinical-manufacturing phase lead to products that are less robust and less operationally friendly.

A CDMO develops products for all sizes and types of companies, and therefore, sees different perspectives and strategies for applying QbD to product development. As key players in industry, CDMOs need to support moving the QbD initiative forward by helping sponsors see potential benefits, so they will give QbD a higher priority and clearly understand the risks of not implementing a QbD strategy. A CDMO can design a phase appropriate QbD strategy to build quality into the product being developed or transferred. Because products arrive on the doorstep of a CDMO in various states and at various phases in the product development lifecycle, complete background information is needed by the CDMO to make

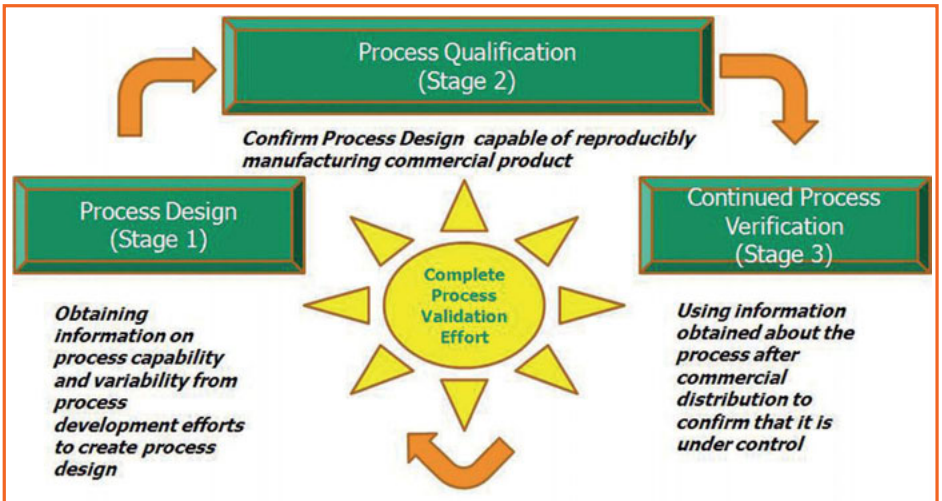

Figure 1. This figure is based on ICH Q8, Q9, and Q10 as well as the most recent FDA Process Validation Guidance and illustrates the various phases in a drug product lifecycle (1).

an accurate gap analysis and assessment of work to be performed for successful transfer and commercialization. A knowledge transfer review is the first step in any successful CDMO QbD program design. As part of the knowledge transfer cycle from development to commercialization we need to review the progress made at each stage of a product lifecycle. The review should first ascertain the desired Quality Target Product Profile (QTPP) for the product.
The QTPP is defined as the prospective summary of the quality characteristics of a drug product that will ideally be achieved to ensure the desired quality outcomes, taking into account safety and efficacy (ICH Q8) (2-4). After determining the QTPP, we would look at the stage 1 Process Design progress and outcomes. In particular we would examine the status of identification of the CQA's, as well as the level of understanding of the CPP's interaction and influence on these CQA's. The Process Design Space developed in stage 1 creates the template for process scale up and qualification efforts in stage 2. In this Process Qualification phase, a CDMO would want to determine if the sponsor has successfully confirmed that their Process Design Space is capable of reproducibly manufacturing the commercial product. If gaps exist at this phase, reverting to stage 1 and repeating some Process Design work may be necessary. Lastly, in stage 3, we would evaluate sponsor experience with Continued Process Verification, in which a system is set up to evaluate process control and facilitate recognition and intervention in cases of product performance changes due to process, equipment and/or material variation.

Designing of a risk ranking tool based on a knowledge base mapping exercise (figure 3) can help to guide CDMO/sponsor discussions on next steps and optimal QbD strategy. Risk of product robustness can be evaluated by examining progress and remaining risk areas based on the aforementioned product development lifecycle categories:

1. Process Design (Product Knowledge)
2. Process Qualification (Verification of Process Understanding)
3. Continued Process Verification (Monitoring and Control Strategy)

Once gaps and risks have been identified utilizing knowledge base mapping and risk assessment tools, the CDMO can design a phase appropriate QbD strategy to verify the optimal process

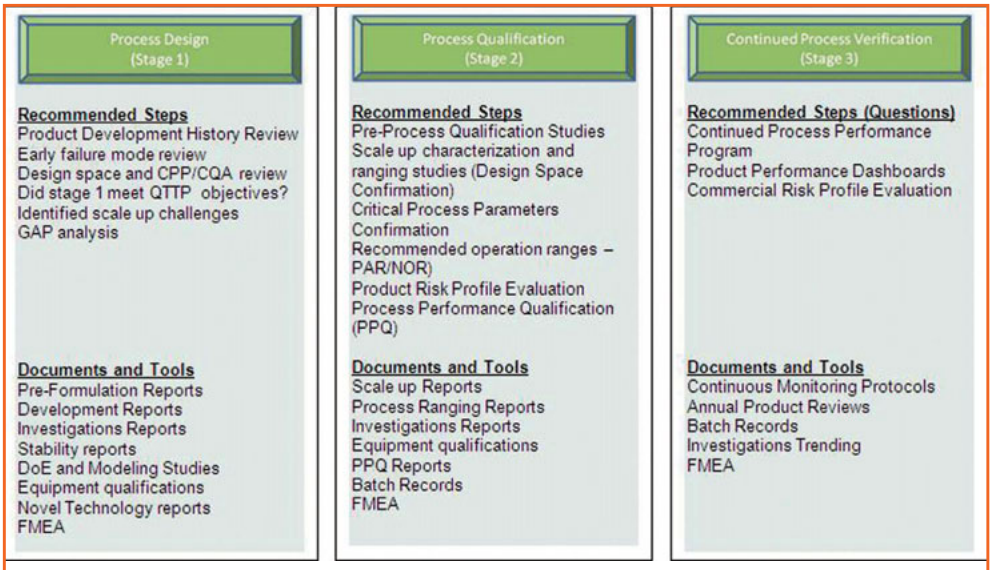

Figure 2. This figure represents recommended steps for knowledge base mapping and documents and tools that can be examined and used to identify risks and gaps in the product QbD program.

Overall Risk Level	Criteria
Severe	All categories have high risk ratings
High	2 at high or 2 medium and 1 high
Moderate	3 with medium or 1 with high
Low	1-2 with medium and others low
Minimal	Low risk for all

Figure 3. This figure represents and an example of a possible risk ranking tool used in a QbD assessment strategy

Factor	A	B	C	D	E	F	G
RUN #	Spray Time	Impeller Speed	Chopper Speed	Wet Massing Time	Dry LOD	Dry Screen size	Talc Blend Time
1	3	150	1800	0.5	1	32	5
2	3	150	1800	0.5	1	45	15
3	3	150	3600	2	2.5	32	5
4	3	450	1800	2	2.5	32	15
5	3	450	3600	0.5	2.5	45	5
6	3	450	3600	2	1	45	15
7	10	150	3600	2	1	32	15
8	10	150	3600	0.5	2.5	45	15
9	10	150	1800	2	2.5	45	5
10	10	450	3600	0.5	1	32	5
11	10	450	1800	2	1	45	5
12	10	450	1800	0.5	2.5	32	15

Figure 4. This figure illustrates an example of a small scale DoE study used for better understanding of a transferred high shear/fluid bed granulat ion process prior to execution of commercial scale transfer trials.

to baseline and monitor commercial process performance (5). Figure 4 illustrates an example of one small scale DoE study used for better understanding of a transferred high shear/fluid bed granulation process prior to execution of commercial scale transfer trials.

With post commercial technical transfers, especially older, established products, the challenge is often in knowing where to begin. For these transfers a similar knowledge base mapping would occur to assess process capability with respect to customers' requirements, the understanding of true process variability, analysis of process robustness, and confirmation of the adequacy of the existing control strategy. Approaches similar to those listed earlier for new products or pre-validated processes, where quality is designed into the process – can also be leveraged for existing or legacy products to enable successful transfer, optimization, commercialization, and ultimately Continued Process Verification.

design space to be used for commercialization. If a sponsor project is initiated in stage 1 (Process Design) the QbD program can follow normal pathways with identification of CQA/CPP relationship and development of Design Space as key outputs for the initial trials. If the sponsor project is part of a later stage transfer, the risk assessment and knowledge gap analysis may lead the CDMO to recommend scaled-down Design of Experiment (DoE) studies intended to challenge and verify the existing process space to ensure material, equipment, and/or process CQA's and CPP's are aligned and able to meet product quality targets. Once confirmed, the CDMO would then verify optimal process design space through qualification activities, and follow up by addressing identified risks assessment outcomes to ensure a robust Continuous Process Verification strategy was developed

Another challenge for CDMO's in designing QbD programs for sponsor products is in open communications and sharing of key documentation (development history, deviation history, CMC filing information etc). Although we have shown that effective knowledge base mapping is critical to the success of any sponsor QbD program at a CDMO, many sponsors concerns over information sharing even outweighs their concerns over delays to timeline, or increased cost (figure 5) (6). As shown, effective knowledge base mapping is the first step in any CDMO QbD program, and access to a transferred products development and commercial history is key to the QbD program's success.

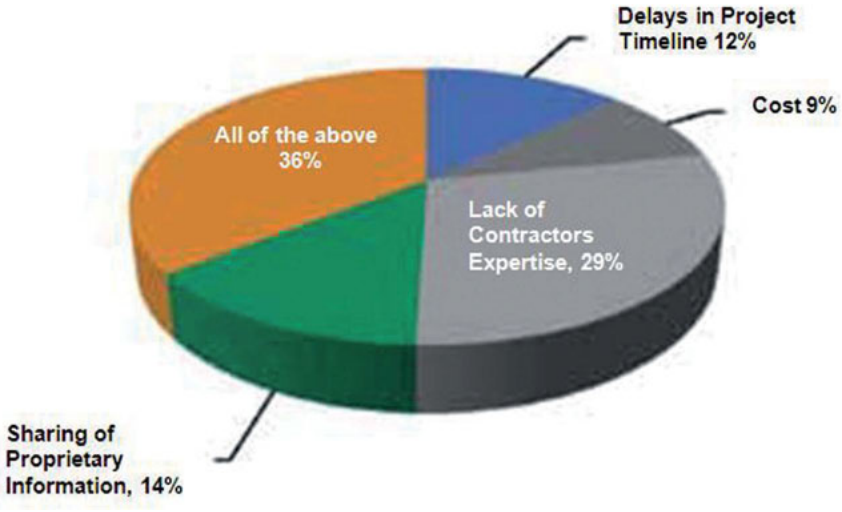

Figure 5. This figure represents examples of sponsors concerns in executing a QbD program with a CDMO (taken from poll conducted as part FDA/Xavier University Global Outsourcing Conference (Cincinnati, OH, USA 2011).

Not only is complete information sharing and transparency key to an effective QbD program, and ultimately a products success at a contract manufacturer, recent regulatory offerings outlining requirements in outsourcing arrangements would suggest it is mandatory. In January 2013 the EMA revised cGMP regulations went into effect including Chapter 7 on Outsourced Activities. According to the regulation, as the "Contract Acceptor", a CDMO should "ensure all products, materials, and knowledge delivered to him are suitable for their intended purpose". QbD elements are incorporated by

definition into the phrase "all information and knowledge necessary' found repeatedly in Chapter 7 (7).
In May 2013 the FDA issued its draft guidance, "Contract Manufacturing Arrangement for Drugs: Quality Agreements," with recommendations on its "current thinking on defining, establishing, and documenting the responsibilities of each party (or all parties) involved in the contract manufacturing of drugs subject to Current Good Manufacturing Practice (CGMP). The FDA draft guidance makes it clear that a CDMO which would normally have to comply with cGMP's, may still be in trouble for allowing an unsafe or ineffective product to be produced at their facility or a non-compliant process to continue to be followed (8). The increased regulatory scrutiny should stimulate increased collaboration between sponsors and CDMOs, especially with regard to visibility on process performance and the exchange of key process and quality historical data, which are essential to continuous improvement and maintaining the state of validation in an outsourced manufacturing environment.

CONCLUSION

With product development and manufacturing increasingly being outsourced to contract development and manufacturing organizations, a strategic partnership between the sponsor and a CDMO can help realize the benefits of QbD. Quality by Design should be viewed as an opportunity to bring value and business benefits to both the sponsor and the CDMO. The CDMO Quality by Design program works with the sponsor to address critical issues pertaining to product quality and the process early in the product lifecycle. This requires a formal plan at the start of the QbD program, based on knowledge base mapping and risk assessment, and both the CDMO and the sponsor need the commitment to do the work upfront. Challenges may still exist, especially related to sponsor concerns over timelines, cost, and information sharing. However, being encouraged by the current regulatory environment, the sponsor and CDMO need to facilitate effective collaboration across organizations to ensure that improvements are identified and implemented through effective communications and an environment of mutual trust. This strategy enables a seamless QbD implementation when the sponsor and CDMO work in synchronized fashion for successful commercialization of the product.

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