Quality by Design: A Peptide CMO Approach

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Implementation of Quality by Design (QbD) is a challenge as well as a necessity in order to be successful in a business where competition is increasing and timelines are ever more challenging. This paper shortly describes the ideas and principles we are working according to in order to shorten development timelines as well as develop robust processes.

What is Quality by Design?

Both the PAT (Process Analytical Technologies) framework[1] and the Pharmaceutical Development guidance[2] recognize that "quality cannot be tested into products; it should be built-in or should ***be*** by design." PAT is a system "for designing, analyzing and controlling manufacturing through timely measurements (*i.e.* during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."[1] While the PAT framework describes analytical systems and methodologies, the guidance on Pharmaceutical Development provides the philosophy behind these tools.

In short, QbD is about

- enhancing process understanding and process knowledge by structured, systematic experimental work, *i.e.* enhanced cause-effect understanding and understanding of parameter interactions;
- defining the Design and Control Spaces of the process, in which critical process parameters and operating ranges are identified and controlled;
- enhanced understanding of process variability and which sources of variability that are critical;
- designing quality into the process so that variability is managed by the process.

What are the benefits of QbD?

- QbD maximizes value; QbD is considered to be the pharmaceutical industry's equivalent to six σ;
- QbD manages and reduces risk;
- QbD provides efficient lifecycle management, *e.g.* by enabling continual process improvement within design space without regulatory assessment of post approval changes.

How has PolyPeptide implemented QbD?

There is additional complexity when we apply the QbD approach at PolyPeptide due to the extensive processes we employ in the production steps for the manufacture of peptide API. This compels us to be selective in characterizing the steps requiring a design space. PolyPeptide focuses attention on our critical process steps such as cleavage-deprotection, oxidation, purification, isolation & lyophilisation; the corresponding critical parameters are thoroughly challenged. The Solid Phase Peptide Synthesis assembly requires further attention for design space as it is necessary to employ PAT on line and PolyPeptide will continue its efforts in QbD in this challenging area.

Defining Quality Attributes of a Process

Although the CQAs (Critical Quality Attributes) of the product have the most prominent place when designing a process, it is not sufficient to design a process only with the CQAs in mind. The scope of the quality concept has to be expanded to encompass all quality attributes of a process, which are:

- Critical Quality Attributes of the product;
- Yield;
- Throughput (*e.g.* kg/day);
- Costs;
- Robustness (*e.g.* scalability, reproducibility, lack of deviations, out of specifications, out of trends, reprocesses, reworks *etc*).

Clarifying Process Development Objectives

Process Development objectives typically change over time; for example, the initial CQAs for material intended for toxicological studies are almost never identical with the CQAs for the commercial drug substance, neither are the throughput and cost requirements the same over the product's lifecycle. In order to be able to develop a process fit for purpose, the objectives for each development phase must be unambiguous. It is therefore important to put numbers on the Quality Attributes of the Process that is about to be developed, *e.g.* quality of the product, process capacity and costs. For strategic purposes it is necessary to have initial projections of future requirements.

Working with Process Development Strategies

A process development strategy should be aligned with a regulatory strategy as well as with a manufacturing strategy including a strategy for meeting generic competition. The purpose of establishing a Master Process Development Plan at a strategic level would be to proactively plan for continual process improvements even after approval in order to remain competitive. A plan would include a set of actions and triggers. The actions would be development plans for each process step not on the ideal route for commercial manufacture, see *Figure 1*, and plans for active removal of existing obstacles and constraints, and the triggers would typically be changes of objectives, removal of constraints, new constraints, but also acquired knowledge and experience about the product and process.

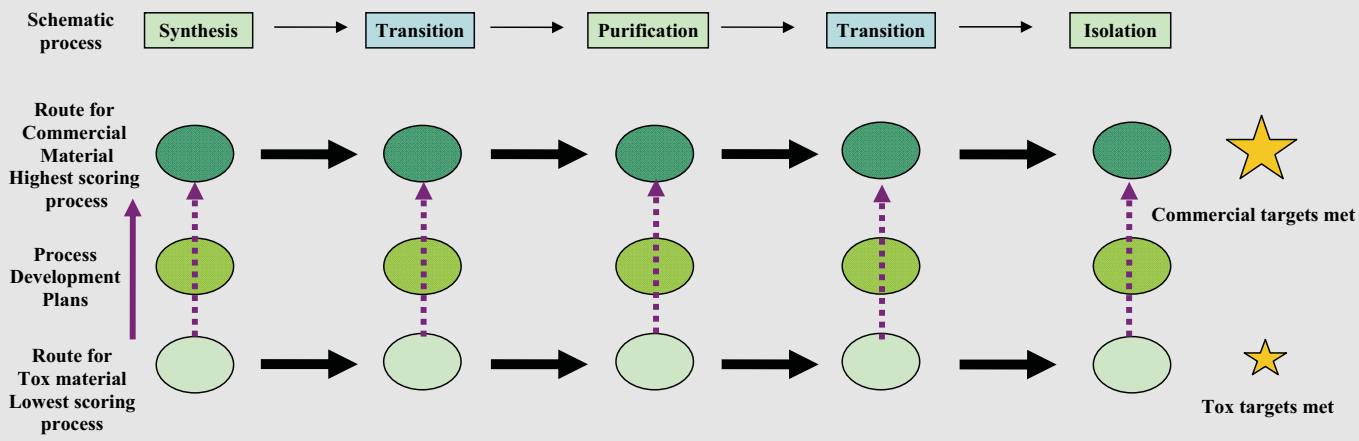

Figure 1. *Conceivable Process Routes for a schematic process; the higher the score the closer to a commercial process.*

Thorough Process Assessment and Planning

Initial process assessment and route selection are often based on mechanistic models, prior knowledge and accumulated experience, although experimentation is almost always required in the end to support route selection and to reduce project risks to acceptable levels. However, in order to be able to make the best balanced decision on the process route, decision analysis tools can be applied - where objectives are classified as either musts or wants and weighted total scores are calculated for each alternative, and where risks for each alternative are identified and assessed according to their probability and seriousness. In this decision process it is therefore extremely important to clarify short and long term objectives as well as all existing constraints.

Once selection of a viable process route or routes has been made, a risk assessment[3] at a more detailed level should be performed in which each high to low level process parameter is scrutinized and assessed whether it is a no, low, medium or high risk parameter regarding the impact on quality attributes of the process. If there is no risk the parameter can either be kept constant or can be considered to contribute only noise.

After completion of this exercise the planning phase of process development can begin using the risk assessments for prioritizing the studies and the key question to answer will be:

How to minimize the risk of failure and maximize the probability of success?

For medium or high risk unit operations Design of Experiments (DOE) is recommended both to identify important operational parameters with high impact on performance parameters and to define safe operating ranges with respect to the quality attributes of the process. The more assumptions and the more unit operations or operational parameters left uninvestigated, the higher development risk and the higher risk of failure later.

Dividing Process Development into Distinct Phases

In a QbD approach the Design and Control spaces of the process, in which critical process parameters and operating ranges are identified and controlled, should be defined before end of Clinical Phase III filing, see *Figure 2*. This work is performed during the Optimization and Robustness testing phases. The process should therefore be ready for Process Validation[4] by mid to end of Clinical Phase III.

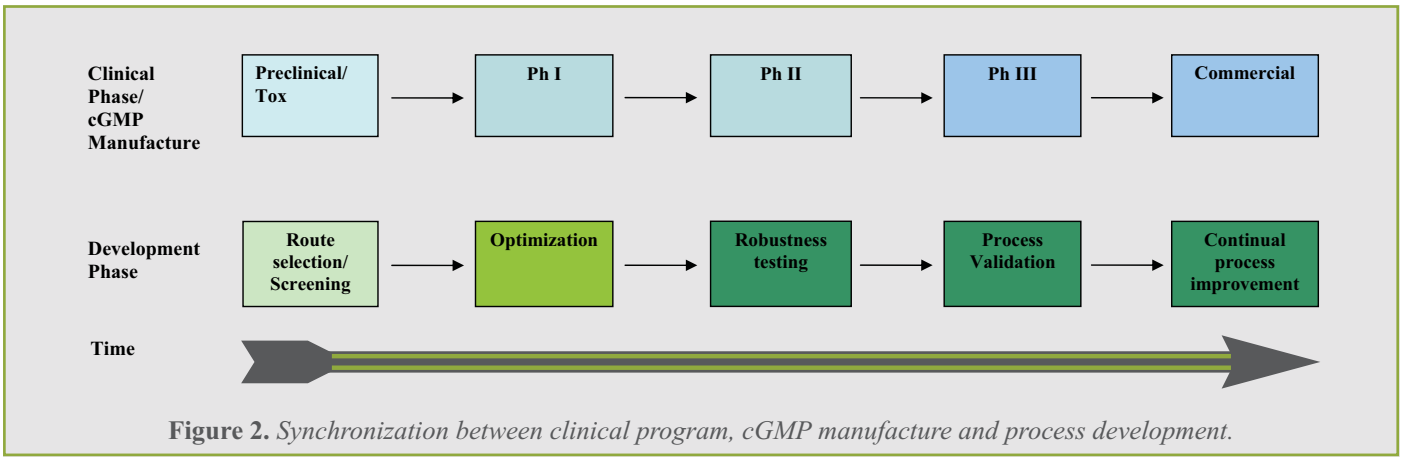

Figure 2. *Synchronization between clinical program, cGMP manufacture and process development.*

Recognizing Important Prerequisites for Process Development

Since time always is a constraint, efficient time management is a key success factor for developing processes with minimal risk and maximal value. The combination of a QbD approach, *i.e.* structured, systematic experimental work aiming at enhanced cause-effect understanding, and high throughput experimentation provide an ideal basis for achieving efficient use of available development time; but it is not without effort and it requires both strategic investments in infrastructure and training as well as a systematic removal of bottlenecks, which are slowing down the development work. All development work can be divided into sub-phases, and each sub-phase and transition between sub-phases can be scrutinized for bottlenecks and be subject to optimization, see *Figure 3*. Since process development efficiency can be expressed as a function of cycles per time, much can be gained by cycle optimization.

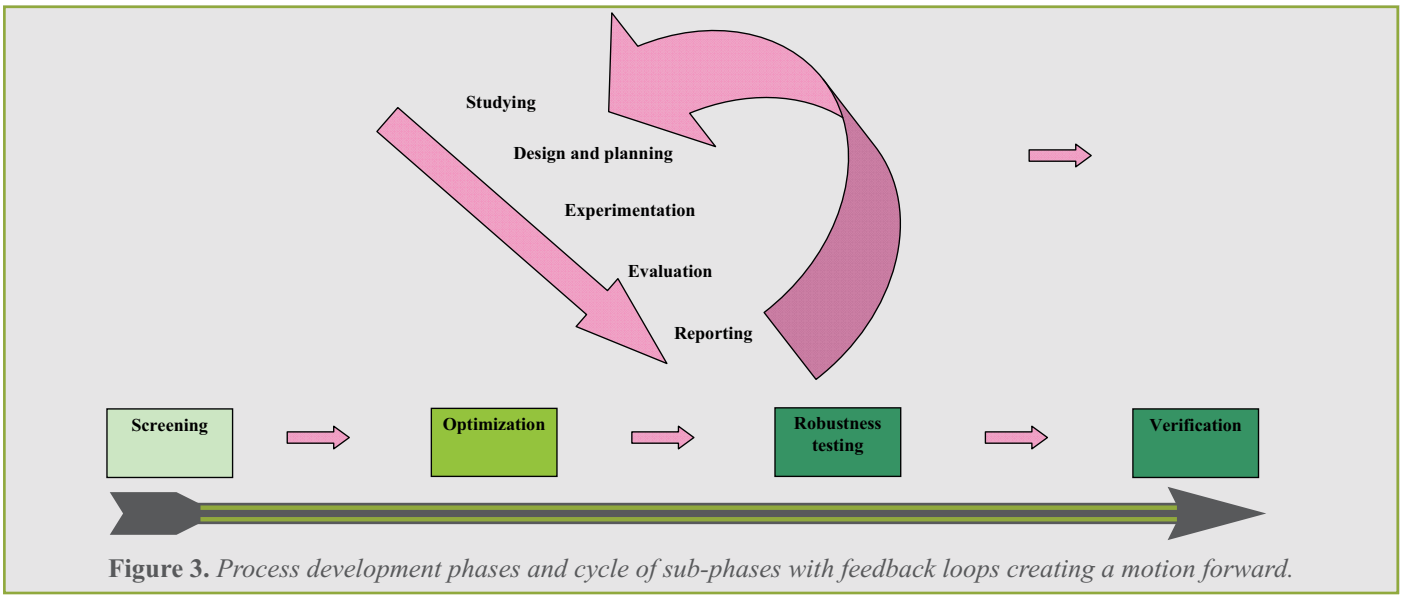

Figure 3. *Process development phases and cycle of sub-phases with feedback loops creating a motion forward.*

What are the prerequisites for an efficient process development, i.e. reduction of cycle time? What infrastructure is required to accommodate many experiments with fast iteration and feed-back loops?

Instrumentation- the use of lab robots for synthesis/purification/isolation as well as high capacity analytical systems would allow for high capacity experimentation and analysis.

Information Technology- should be used to provide efficient exchange of information and knowledge from internal and external databases and efficient handling, *i.e.* logging, transformation and reporting of experimental data generated by HTP instruments. The use of electronic notebooks in combination with laboratory information management systems would for instance enable real time archiving of raw data and real time build-up of internal searchable databases.

Prediction and Design tools- Prediction tools can be either mechanistic and/or empirical, and the better *in silico* tools the better virtual product and process assessment can be made early on. The use of DOE (Design of Experiments) in combination with MVDA (Multi Variate Data Analysis), *i.e.* construction of PLS/ PCA models, has the potential of turning large data sets generated by HTP (High Through Put) experimentation into useful information that can be fed back into the investigation and thus enhance process understanding.

Organisation and training- in order for PR&D (Process R&D) to be proactive and to be able to respond to current as well as future requirements its scientists should be encouraged to continually develop and increase their competences and skills and they should be allowed to be in a constant state of learning and to investigate and implement new technologies well ahead of need.

References

[1] Guidance for Industry, PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

[2] Guidance for Industry, Q8 (R1) Pharmaceutical Development

[3] Guidance for Industry, Q9 Quality Risk Management

[4] Guidance for Industry, Process Validation: General Principles and Practices