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IMPORTANCE TO BECOME A *FAN* OF QUALITY BY DESIGN (QBD) AS EARLY AS POSSIBLE DURING DRUG DEVELOPMENT

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Over the last decades, timelines to enter into Phase I clinical trials are becoming increasingly shorter as companies seek definitive results that would prove or disprove their drug's potential. In parallel, drug substances became more and more difficult to formulate due to their poor biopharmaceutical properties (solubility, permeation, absorption and bioavailability). Formulation development has become the crux of the matter to develop a formulation that will be stable, reliable, and where it will represent, as much as possible, an almost final formulation. More precisely it means that formulated dosage form should not generate the carrying out of comparative bioavailability studies between the clinical phases, to narrow down the cost and especially the time of development. Quality by design (QbD) became a powerful tool to achieve this goal with success and has already demonstrated its reliability not only with marketed products but also at the early stage of development where, most of the time formulation development is step that has been (and still is) plus or less neglected because of the lack knowledge in that domain.

Gathering the maximum information with regards to safety, efficacy and galenic aspects of the drug during early stages of development is often a challenge when faced with stresses of aggressive timelines, financial constraints and investor milestones. Since the cost associated with clinical trials accounts for a significant portion of the overall drug development prices, it is not surprising that the main focus is to ensure that the clinical trial is designed and developed as close to perfection as possible. Most of the time however, the other half of the project (i.e. the development of the actual drug product), is not given the same level of attention despite the increasing poor "druggability" properties of modern-day Active Pharmaceutical Ingredients (API)... For most emerging companies, critical time is defined by the start date of "First-subject-dosed". Typically, these dates are fixed by the team planning the clinical trial. Actual supply of drug product is more often than not an afterthought…In a rush to supply a drug product, concessions on formulation development are often made (or simply delayed until a later date), without correspondingly moving out the clinical start dates. The downside with such an approach is that clinical testing may be initiated with a less-than-optimal formulation for which reliability, reproducibility, and scalability are not fully understood. Keeping in mind that the focus of Phase I testing is mainly to evaluate safety, additional bridging studies maybe requires later on when clinical results turn out to be promising.

The question that arises is: Does this really accelerate the overall development process? The best scenario would try to be ahead of timelines when a sponsor enters in first-in-humans/patients study. Quality by Designed (QbD)(1-3) is then proposed to narrow down the chances of changing the formulation attributes during drug development. As an example, by initially developing a formulation that will represent almost 80% of the final product, fewer comparative bioavailability studies will have to be performed, and it will be more difficult for the formulation to be held responsible for any unexpected results, such as poor reliability, non-reproducible pharmacokinetic and thus pharmacodynamy.

The author of this short commentary will try to "popularize" as much as possible what QbD is for start-ups so they keep in mind that due to new molecular entities becoming more and more difficult to formulate, QbD should become their most reliable ally for early drug development and beyond.

Given its direct impact on the overall development program, it is imperative that a thorough early drug development approach with a long-term view be adopted and integrated as early as possible.

Each scientific discipline (pre-clinical, pharmaceutical R&D, clinical, etc.) should work very closely, not sequentially, to maximize chances of not only bringing a new drug successfully into clinic, but also to anticipate and plan for challenges that may come in later phases of development.

QbD can (and should) be defined as follow,

- A process understanding that will allow to understand the formulation development/manufacturing process, based on a thorough understanding of the preformulation, formulation and quality risk management
- An exercise that is expected by regulatory agencies
- An excellent holistic approach, since multifunctional steps will be treated by people coming from different area, such as preformulation/formulation, engineering, manufacturing and analytical development
- A deep quality system for product's lifecycle management

The overall above bullets are illustrated in the schematic representation below.

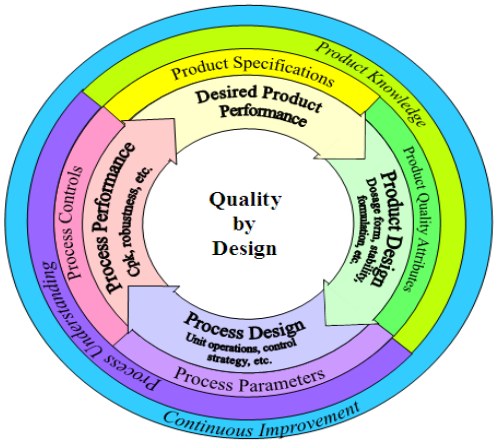

Figure 1: Schematic representation of QbD[4]

According to section Q of ICH guidelines[5], product life cycle management can be defined sequentially as follow.

- **Product design**: When the new molecular entity is selected, formulation of the dosage form is determined.
- **Process design** will then take place and critical process parameters (CPP), critical quality attributes (CQA) will be determined.
- **Scale-up and transfer**: Once the above process is determined, formulator and engineers should share their knowledge based on the CPP and CQA, to streamline as much as possible the impact of scale - up, even though the same qualitative equipment is used (as an example, mass transfer and heat transfer will change over the scale). This step is crucial during scale-up. Engineering batches will be manufactured under large scales (like commercial batches); CPPs and CQAs will be challenged to the fullest extent.
- **Commercial manufacture**: Surprises should not be expected anymore at this step of manufacturing, the QbD having narrowed down by far any risk of unexpected results.

The following ICH Q guidelines will cover.

- ICH Q8/Q8R, Pharmaceutical Development will cover **product** and **process designs**, **scale-up and transfer**.
- ICH Q9 – Quality Risk Management will cover **product** and **process designs**, **scale-up and transfer** and **commercial manufacture.**
- ICH Q10 – Pharmaceutical Quality Systems will cover **process design**, **scale-up and transfer** and **commercial manufacture.**
- ICH Q11 – Development and Manufacture of Drug substances will cover **product** and **process designs**, **scale-up and transfer** and **commercial manufacture.**

Figure 2 below illustrates the traditional formulation manufacturing approach versus the QbD approach.

Aspects	Traditional	QbD
Pharmaceutical development	Empirical; typically univariate experiments	Systematic; multivariate experiments
Manufacturing process	Fixed; validation on 3 initial full-scale batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy and robustness
Process control	In-process testing for go/no-go; offline analysis w/ slow response	PAT utilized for feedback and feed forward at real time
Product specification	Primary means of quality control; based on batch data	Part of the overall quality control strategy; based on desired product performance
Control strategy	Mainly by intermediate and end product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle management	Reactive to problems & OOS; post-approval changes needed	Continual improvement enabled within design space

Figure 2: Traditional versus QbD approach[6]

It should be noted that the traditional approach has demonstrated a proven track record. It would be interesting to have an idea of the cost of non-quality generated by the traditional approach vs the QbD, and to what extent the QbD method has improved the rate of overall process development. Instinctively, considering

what have been presented to date in this communication, both drug product and process development should be better understood, out of specifications batches and batch failures which should happen less frequently, processes being optimized and improved.

Briefly, QbD steps can be summarized as follows.

- Define the Target Product Profile (QTPP)[7] which represents a summary of the quality characteristics of a drug product to ensure safety and efficacy.
- Determine CQAs: "a CQA is 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. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.".[8] CQAs may then be impacted by API, excipients and process variability.
- Performing risk assessment by linking raw Material Attributes (CMA) and CPPs) to CQAs. This is based on scientific knowledge and literature as well as preformulation/formulation experiments. As mentioned earlier, a group of experts such as formulators, analysts, engineers should be working together and generate a systematic process for the assessment, control, communication and review of risks to the quality of the drug product, irrespective of time and scale.
- Develop a design space (DOE): Based on ICH Q8R2[8], a design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is possible to describe a design space as a time dependent function (e.g., temperature and pressure cycle of a lyophilisation cycle), or as a combination of variables such as components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can contribute to establish a design space. Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality."
- Design and implementation of a control strategy: "Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely feedback / feedforward and appropriate corrective action and preventive action".[9]
- Manage product lifecycle, including continual improvement. Till based on ICH Q10, "in order to evaluate, approve and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements".

However, based on the above, one can see that Quality by Design, being something under perpetual improvement, shows some advantages and limitations. Advantages are listed below.

- The first advantage should make the whole development process more efficient, irrespective of the drug substance, drug product. How? As described above by generating an overall better understanding of both the product (API, drug product) and process(es).
- It should then improve manufacturing efficiency by predicting pitfalls and reducing variability of the manufacturing process that may happen for the whole supply chain.
- The result will be an increase of quality, a reduction of non-conformity cost, by decreasing batch failures and any kind of problem related to process development. The final result will be an overall optimization of process improvement.

Concerning limitations, some of them are listed below.

- As mentioned above, scale-up may imply the use of different equipment, not only from a quantitative but also from a qualitative standpoint. At least, when the same kind of qualitative blenders (as an example) are used, it may be easier to reproduce the whole behavior of the process, if excipients, APIs, conditions of operation remain the same.
- The following may represent a paradox with all the above however, the QbD approach at its early formulation development stage (phases 1-2), even though very important, may not be so reliable during scale-up, especially if equipment is to change, since new MPPs will have to be determined. Furthermore, unexpected results may happen, coming from the API during scale up, such as new polymorphic form and particle size. DoE may then change and so will the QbD approach.

CONCLUSION

In this communication, a summary of the QbD has been exposed. Of course, an overflow of documents is available in literature, with accurate examples of how QbD may vary depending on scale and dosage form. However, in all the cases, and as described in this current paper, it is crucial to.

- Gather as much data as possible on the physico-chemical characteristics of both the API, and the excipients.
- Determine the MPP based on the process that will be used.
- Keep as close as possible to the same formulation process development to avoid any changes in the

MPPs, understanding the CQAs may change because of a new process.
- Implicate as early as possible all the people working in the overall drug development process, meaning not only the formulators and analysts, but also all involved in analytical technology and pharmaceutical engineering in order to mitigate risks and stay on top of pitfalls that may occur down the road of drug development.

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