DOES QUALITY BY DESIGN HAVE THE 'X-FACTOR'?

by By Line Lundsberg-Nielsen & Bruce Davis

1. QbD – ROBUST PROCESSES AND THE 'X-FACTOR'!

We are all probably aware of some non-robust processes in the pharmaceutical industry. We also know that our industry rarely operates at a Six Sigma level – a standard many other industries achieve. Why is this? Are we too focused on compliance? Has having the occasional reject batch become the norm?

So, can an 'X-factor' be found to bring back higher efficiencies, create less waste and produce more effective products? Quality by Design (QbD) might or might not be the 'X-factor', but it does provide an opportunity for our industry to do things differently, to do them better and to have more robust processes.

2. QbD – PATIENT FOCUS

QbD has become a 'buzzword' to represent the science and risk-based quality paradigm, as expressed by the ICH Q8, Q9 and Q10 guides. The QbD concept focuses on how to develop and manufacture pharmaceutical products by applying a science and risk-based approach throughout the entire product lifecycle, from early development through scale-up, technology transfer and commercial manufacturing to product discontinuation. The key to QbD is product and process understanding based on what is critical to the patient in terms of safety, efficacy and quality.

One might ask "Isn't this what we have always done?" and the answer is probably "Yes and no". Certainly, patient requirements have always been central when developing new medicinal products, as has the application of science. The traditional approach has, in broad terms, involved developing the API and formulated product for early clinical trials and then scaling-up for commercial manufacture with a focus mainly on compliance and end-product testing. Probably lacking has been a continuous thread of key information from early laboratory work to full scale manufacture.

The QbD approach aims at establishing a more comprehensive understanding at all stages by focusing development activities on what is critical to the patient, then controlling these critical aspects during commercial manufacture. Once a product enters commercial scale manufacture, very significant quantities may be produced before errors are detected using conventional end-product testing, or the error may not be detected and reach the patient before being discovered. By enabling real time monitoring of manufacturing the QbD approach offers significantly improved assurance of product quality for patients.

3. QbD – A SCIENCE AND RISK-BASED APPROACH

For developing a new product, the QbD methodology can be described in simple terms as a series of iterative steps as below:

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- Defining the Quality Target Product Profile (QTPP) = patient requirements
- Understanding the Critical Quality Attributes (CQAs) = the product attribute specifications
- Defining Critical Process Parameters (CPPs) = the process parameters that impact the CQAs
- Establishing the Design Space = a new way of describing ranges of CPPs and attributes impacting the CQAs. If a process is operated within this space, the CQAs are assured
- Developing the Control Strategy = the actions necessary to ensure the manufacturing process remains within the Design Space
- Enabling Continuous Improvement = making improvements throughout the product lifecycle

These steps are supported by risk assessment, knowledge management, and by PAT tools, which provide techniques to monitor, adjust and control processes in real-time.

4. QbD – MOVES CONTROLS UPSTREAM AND INTRODUCES REAL TIME RELEASE TESTING (RTRT)

Relying on end-product testing is too late if during manufacturing anything has gone wrong. Both patients and business might be at risk, for example patients could face a product shortage and the manufacturer could lose business. A QbD control strategy ensures the product will comply with CQAs specified. PAT techniques enable the process to be controlled in real-time by using in-process information to predict settings of upstream equipment. This approach has, to a certain extent, always been utilised for aseptically produced sterile products, where meaningful end testing of the sterility CQA is not possible. QbD extends both the depth and scope of this approach, by requiring greater mechanistic understanding of processes and going beyond sterile products to include the manufacture of all dosage forms and other CQAs.

An example is a drying process. Drying time depends on the initial and final required moisture level of the process material. This may seem obvious, but many drying processes have traditionally had a fixed drying time and rely on sampling and off-line QC testing of the moisture level. In QbD the initial moisture level may be used to set the drying process parameters and then on-line NIR used to measure the level and feed this back to the process to enable drying to be stopped when the material has the correct moisture content. By moving these controls upstream in the overall process, it enables these to be used for RTRT and potentially avoid testing at the end. Not only does this create savings in QC activities but also improves production cycle time and hence enables cost efficiencies to be made.

5. QbD – AND THE ROLE OF THE QUALIFIED PERSON (QP)

At first glance, QbD seems to be much more complex than the conventional approach, for example by applying PAT tools with multivariate data analysis and mathematical models. However, with an enhanced level of process understanding, it becomes easier to assure the quality of the product. The control strategy serves as one of the guiding tools that the QP can use when reviewing batch documentation, to provide them with greater assurance that the CQAs have met specifications.

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6. QbD – IMPACT ON SMALL COMPANIES AND GENERICS

In broad terms 'Big Pharma' companies seem to have embraced QbD and many now take a strategic approach and organise their internal development and manufacturing processes to support QbD. What about smaller and generic companies? Where is the value for them?

Such companies generally do not have resources or time for large R&D investments, as being first in the market place is such a key business driver for them. But to have more robust processes and greater clarity about safety and efficacy are strong business motivators. Smaller companies can gain by 'cherry-picking' the parts of the QbD that give the maximum benefit. For example, it may be too costly to establish the full design space, but investigating a difficult unit operation to make it more robust may create an immediate business benefit.

7. IN CONCLUSION

Whatever the future for QbD, it certainly has brought logic and clarity about how our products should be developed and manufactured. It has also raised the importance of ensuring development and manufacturing departments work closely together.

QbD will not only provide business efficiencies but, most importantly, will continue to benefit patients. Yes, QbD really can provide the 'X-factor'!

ABOUT THE AUTHORS

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