QbD and Risk based approach for efficient design of Pharma Plants

One of the major challenges faced by Pharma plants globally is getting regulatory approvals and maintaining them. Many plants especially in India are losing their FDA certification during audits due to gaps in documentation and the constant complaint of pharma manufacturing companies is the convoluted and excessive documentation required.

Actually the FDA and the global Pharma community has adopted the Risk based approach to Qualification and Validation which leads to much more clearer and less voluminous documentation. It is high time that the India pharma industry also adopts this approach in a more aggressive manner.

The purpose of this article is to elaborate the QbD (Quality by Design) and Risk based approach during project execution.

Concerns with conventional approach

Conventional approach relies almost revolves around testing of end product quality. While this ensures uniform product quality to consumer, it does not address underlying issues related to deviations in quality. To reach an uniform product quality it resorts to a cumbersome Commissioning, Qualification and Validation process with a very heavy focus on generation of excessive documentation and long paper trails. While from a project execution perspective this substantially inflates the project schedule. While a conventional chemical plant would take 14-18 months from concept to start-up , a similar complexity Pharma plant would take anywhere upwards of 3 years. Post startup the plant operations and QA get buried in mountains of procedures and documents. This gives the auditors ample ammunition to identify non-compliances and further to cancel FDA licenses.

And just ask anyone to make a modification in the plant post qualification and it looks as if a disaster has befallen then. Even the biggest of optimization opportunities are knocked off due to regulatory constraints.

The QbD approach

So how does the QbD approach help? The QbD approach was proposed by FDA at the start of the 20^{th} century as a methodology to do away with empirical methods in the Pharmaceutical industry and bring in a more scientific and engineered approach. Quality by Design starts right at the drug development stage. The core of the process are CQA(Critical Quality Attributes) and CPP(Critical Process Parameters).

Critical Quality Attributes (CQA) are chemical, physical, biological and microbiological attributes that can be defined, measured, and continually monitored to ensure final product outputs remain within acceptable quality limits. In simple words these are the quality parameters which would have a direct impact on the drug efficacy.

Critical process parameters (CPP) in pharmaceutical manufacturing are key variables affecting the production process. CPPs are attributes that are monitored to detect deviations in standardized production operations and product output quality or changes in Critical Quality Attributes.

One example of CQA could be the dissolution of tablet. Lower dissolution of the tablet could reduce the efficacy of the tablet and a higher dissolution could potentially cause side effects. This needs to

be established in the early stage development of the product. Once this value is established , the process parameters which could affect the dosage need to be assessed.

CPPs are then identified for each process step. For example for the manufacture of tablets one of the key manufacturing steps would be Granulation. The CPPs for Granulation would be excipient properties, water content post granulation and particle size.

Once the CQA and associated CPPs are identified, the next step would be to identify the Design Space. Design Space is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. In simple language , it is the range of values within which the CPPs can be varied keeping the CQA within acceptable range.

The design space gives the clear criteria for the design of individual Unit Operations. Operating within the design space does not involve a change and provides greater flexibility in operating within the FDA regulatory constraints. Only if the operating regime is moving outside of the Design Space regulatory change management process is required.

Design Space can be defined by using three methods

a. Process Modelling – Using first principles of Chemistry, Physics and engineering to create a process model and predict the design space.
b. DOE (Design of Experiments)- Using statistically designed experiments to assess interactions of multiple parameters. This method is most reliable but can be quite time consuming and expensive.
c. Scale up – Use of semi empirical correlations to translate lab conditions to commercial scales. This might also involve in some cases piloting studies.

Design space definition in most cases might be a combination of any 2 of the above 3 methods.

Now that the first step of simplification is completed with the definition of CQA, CPP and Design Space. The next step and the most important is to carry out a Risk Assessment.

Risk methodology

The conventional CQ&V methodology requires the uniform Qualification and Validation of the complete plant. However the Risk based approach involves assessing the risks associated with each system in the plant with respect to the impact of variation of CPPs on CQAs and classification of each system into

a. Direct Impact
b. Indirect Impact
c. No Impact

Direct Impact system is a system that has a direct impact on product quality. This needs to go through the complete Qualification and Validation exercise.

An Indirect Impact system that is not expected to have a direct impact on product quality, but typically will support a Direct Impact System. These systems are designed and commissioned following Good Engineering Practice only.

A no impact system is one that has as the name goes no impact on Product Quality.

So the main process steps like Mixing, Drying, Reaction would be classified as Direct Impact systems. Also some utilities like Clean Steam and Nitrogen which come in contact with the product may be classified as Direct Impact. Most of the Black Utilities would be classified as no impact systems. Indirect impact systems could be HVAC, cooling water the failure of which could potentially impact the product quality.

Classifying the systems in such a way greatly reduces the load of Qualification and Validation and consequently reducing documentation.

Further streamlining of the CQ&V process by further carrying out the Impact Assessment of the individual components of Direct Impact systems.

Let us consider a Spray dryer system classified as a Direct impact system by the System level Impact Assessment. The system has components – Spray dryer, spray dryer feed pumps, air heater, combustion air system. A further detailed risk assessment of the system can classify the components as critical/non-critical. The classification would potentially be

a. Spray dryer – critical
b. Spray dryer feed pumps – Non critical
c. Air heater – Non critical (This can be done with a robust control on the air heater outlet temperature)
d. Combustion air system – Non critical

So with this classification, only the critical components would need a full CQ&V whereas the non-critical components need only to be handled as per Good Engineering Practices.

With the two level screening, the total plant is drilled down to Direct Impact Critical Components which are the only parts of the plant which would require a full CQ&V.

Choosing the right Risk assessment method

There are many established risk assessment methodologies available for the Pharma Risk management process. Risk Methodology needs to be chosen based on the product and process information available.

a. Basic risk assessment
   If only the basic information on the product and process information is available (for example only identified CQA and CPP), a simple risk assessment method can be applied like cause and effect analysis or fishbone analysis(Ishikawa diagram). These methods are very effective in the initial stages of the project where a quick prelimnary assessment is required and these risk assessments can feed into development of the plant validation strategy.
b. FMEA / FMECA/FTA
   These risk assessment methods can be applied when detailed product and process information is available.
   FMEA (Failure mode Effects Analysis) is a method more focussed on equipment and facilities and their effects on the product and process. In this method the failure modes are identified and risk rated and the risk reduction ideas can be identified for elimination, contain, reduce or control risks. It is very effective to prioritize risks and monitor effectiveness of risk control activities.
   FMECA (Failure mode, Effects and Criticality Analysis) is similar to FMEA but more focussed on processes. The method can be used to identify further risks which require control or reduction.

FTA (Fault Tree Analysis) is most useful when effects of multiple causes of failure are to be assessed. It is a qualitative method and relies totally on the person's/ team's expertise in carrying out the FTA.

c. HACCP and HAZOP
Hazard analysis and Critical Control Points analysis is the most comprehensive and systematic method to assess risks for Pharma units. It identifies and manages risks associated with physical, chemical and biological hazards. The only constraint with this method is that it requires a thorough knowledge of the Product and Process data. The output of the assessment is identification of Critical Control points.
Hazop is used to analyse the risks associated with deviations from design conditions. It is used more for assessing the safety related risks rather than Quality related risks. It can be used for identifying critical monitoring points in the process.

Leveraging manufacturer and construction documents

Conducting the risk assessments and identifying the Direct Impact systems and Critical Components early in the project enables leveraging of documents received from the equipment/ instrument suppliers and also the standard construction quality check documents to accelerate the Qualification process.

Conventionally the qualification process would start only on Mechanical Completion leading to a situation wherein the plant is technically ready to start production but is constrained in doing so due to extended Qualification process.

With the QbD and Risk assessments in place the preparation of IQ dossiers can start as soon as the supplier documents for the Critical components in Direct Impact systems are received. So the IQ process can be done in parallel with the construction activities. The installation reports from the construction team can be added on to the dossier and IQ dossiers can be signed off in conjunction with the Mechanical completion certificates. Also since the entire plant is split into systems, the IQ can be completed sequentially without waiting for the Mechanical completion of the entire plant.

Advantages of QbD and Risk assessment approach

For the manufacturer it leads to a faster time to market with a reduced overall development cost. FDA audits are simplified and risk of non-conformances can be greatly reduced. Plant optimization initiatives can be more easily implemented especially for Indirect impact and No impact systems.

For the regulatory bodies, it makes auditing of facilities easier. They can actually focus on real quality issues rather than on paper trails.

For the end users it provides more assurance on the quality of drugs that they are buying and consuming.

Challenges of the approach

Though the FDA has clearly indicated that this risk based approach is the path forward for the Pharma regulatory process, the uptake of this methodology in India has been slow. There are multiple reasons for this slow adoption of the new methodology.

Firstly most of pharma companies in India are generic drug manufacturers rather than Inventor companies. So the very first step of QbD i.e. identification of CQAs and CPPs becomes a cumbersome and expensive affair.

The second challenge is the fear of change among the Quality Assurance and Operations community. With the ultra strict approach of the FDA auditors the main fear is that any change from established procedure would cause loss of the FDA license and jeopardise production.

The third challenge is the lack of awareness among the Pharma community of the QbD methodology. Sure QbD and Risk assessment are buzz words but there are very few who actually understand the implications of the new method and how to practically start the implementation of the QbD philosophy.

Meeting the challenges

The only way forward for the Indian pharma industry is to quickly adopt to the new FDA norms. The first step towards this would be to increase the awareness among the Pharma community especially regulatory QA. Training should be another area of focus especially for scientists and engineers who form critical links in implementation of QbD. The QbD approach very close co-operation between R&D and Engineering which till date have mostly operated in compartments.

The starting point for greater understanding would definitely be reading and assimilating the key standards namely

a. ICH Guideline Q8 – Pharmaceutical Development
b. ICH Guideline Q9 – Quality Risk Management