QbD Based Formulation Development

The DPT Labs Approach

Q&A

There were several questions asked during the webinar and rather that responding to each privately, we've compiled them all in one document for the benefit of everyone.

Q - Once you have completed the risk assessment for the process, what kinds of studies are performed to mitigate the risks identified? Can they be performed in the lab or pilot lab or do they need to be performed at full scale?

A - Depending on what the risks are, they can be performed in the laboratory. If it is a mixing issue based on equipment scale, you really need to perform it at scale. If it is a raw material factor, this may be preliminarily evaluated in the lab.

Q - Is it possible to accelerate a DoE study when timing is a factor?

A - Yes, by performing such statistical studies such as a fractional factorial design. By doing this, you are decreasing the amount of experiments to perform and looking at the relationships you believe to be integral to the performance of your product.

Q - Of the steps you outlined in preformulation, formulation, risk assessment etc., what is gained in terms of FDA filings – NDA, 502b, etc.?

A - Through performing your QbD risk assessments and DOE evaluations, you will use the QBR format to develop the areas to investigate, as well as trigger your own questions to ask based on your unique formulations. Once you have performed all of the required work to answer these questions, it makes your documentation that much easier, as well as showing the agency that you have done your homework and have a full understanding of your product.

Q - How is the up-front cost of QbD justified through development to going commercial?

A - The upfront cost is ideally recouped later on by not having to make large scale feasibility batches during clinical, registration, and worst of all validation batches. By investigating the raw material CMA's and the most ideal processing methods up front through an organized QbD fashion, you can greatly reduce the risk of encountering unexpected batch results later on down the line.

Q - Among the software available for DOE, could you please tell me advantage of using JMP?

A - Actually, JMP is the only one I have primarily used. It suits our purposes well since it is very user friendly, powerful, and very versatile in regards to outputs.

Q - At DPT, do you usually apply QbD to projects that are transferred from other CMOs and to projects already developed with optimized formulations?

A - The principles of QbD can be applied to everything we do. For Tech. Transfer projects, we can use QbD to study any changes in equipment from one site to another, or and modifications to the raw materials used.

Q - DT applies QBD to non-sterile preparations; however, can DPT do sterile product manufacturing for opthalmics using QbD?

A - Yes, any pharma project that involves formulation and process development activities can employ these practices. An ophthalmic product will be manufactured just like a non-sterile product, and we can most certainly apply QbD to the sterilization process. Whether you are using filtration, autoclave, or any other sterilization methodology, you can set up DOE studies to determine which is best for your product in regards to short and long term stability implications.

Q - Has your QbD approach allowed companies to make post-approval changes in a more streamlined fashion?

A - We have not worked on any post-approval changes that have occurred within the design space of the original filing yet, but are hoping as we become more intertwined with QbD development, this will be a viable option for us in the future.

Q - How important are freeze thaw studies for small molecules which stable at RT and not intended 4°C storage?

A - Freeze thaw studies are performed more for a stress testing tool, rather than a long term storage condition stability indicator. It is very useful tool to understand the robustness of your solubility of your drug substance, as well as an indicator for physical stability of a semi-solid.

Q - IIG limits shall be considered based on maximum daily dose or mg/ unit?

A - I believe it is based on mg or %w/w per unit.

Q - Is excipient/drug substance compatibility required for generic products?

A - We believe so. Based on the FDA QbR Frequently asked Questions, section 2.3.P.2.1.2 Excipients; they outline what evidence supports excipient/drug compatibility.

Q - From a pharmaceutical perspective, is QBD mandatory or optional?

A - While ICH Q8 technically provides QbD as an "enhanced" approach to drug development, it is our experience that FDA is asking for QbD data to be provided in response to FDA questions during the review of many applications. Also, from our experience, utilizing QbD in the development process will provide a much more robust product and process.

Q - Is your DOE a factorial design or Placket-Burman, or other?

A - We typically perform many variations of a factorial design.

Q - What is the impact in costs and time using the QbD approach during product development?

A - QbD can add extra time and cost to a program if it is being performed to address an issue that was not identified early on in the budgeting process. There is nothing wrong with identifying

these potential issues, as long as they are not being ignored and are fully evaluated and assessed.

Q - What rheological parameters are evaluated during initial development?

A - Shear /Stress, Viscosity, Yield point/value

Q - Does DPT Labs apply this approach to projects transferred from other CMOs and formulations already optimized?

A - Yes, we can and do apply this to projects transferred into our labs. We will review and provide a gap assessment of the Technical Transfer report/Formulation development. With this information, we will discuss with our client and determine if the formulation is robust enough to move into a process development scenario, or whether we need to perform and more laboratory work. If more work is required, it will typically be to investigate how best to compound the product in our facilities with our equipment.