Bayesian Approach to the Specification of Design Space in Quality by Design

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The United States Food and Drug Administration (FDA) has recognized that product development is now the weak link in the "critical path" from scientific discovery to commercial drug products. In response, the FDA has instituted sweeping changes on the way pharmaceutical developers and manufacturers conduct their business. Corresponding global regulatory authorities have followed suit. The FDA's Quality by Design (QbD), a risk-based approach, is focused on process understanding including identifying sources of variability, overall reliability and process robustness. From the FDA's viewpoint, the principles of QbD in pharmaceutical development require establishing a clear linkage between the safety and efficacy of the drug product in the patient with its quality as defined by the attributes of the drug product and then linking it all the way back to the process for preparing the drug product.

Central to the QbD approach is the establishment of a Design Space comprised of the "multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." Despite the central role of Design Space, limited prescriptive information is available regarding to how to construct such a Design Space and to demonstrate that operation within it "…provides assurance of quality."

Development and calibration of a Design Space typically involves construction of multiple predictive response surface models corresponding to drug product attributes. The Design Space is constraint by requirements of meeting multiple response criteria. Such multiple response surface optimizations are typically approached using overlapping mean response or by a desirability function. However, these approaches fail to account for the uncertainty in model parameters and the correlation structure of the data. As shown by Peterson (2004, 2008), a Bayesian approach employing posterior predictive distributions addresses both of these limitations.

This presentation will be directed at several case studies illustrating the use of R in conjunction with an assortment of R packages towards the construction of design spaces for representative pharmaceutical products as part of Quality by Design activities. Furthermore, these case studies will illustrate the additional benefits of using the Bayesian approach, including the following:

- providing estimates of the uncertainty in model parameters;
- enabling the use of prior information leading to more efficient adaptive design and experimentation;
- enabling an approach towards robust parameter design;
- providing a figure of merit (probability) for meeting product specification criteria in terms consistent and easy to understand by technical workers operating in a regulated environment;
- enabling a means to establish the reliability of the Design Space; and
- providing a basis for selection of alternate process settings within the design space while ensuring "assurance of quality."

References

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