Integrated application of a QbD Development Approach across Chemical and Formulation Manufacturing Process

Gert Thurau, Merck Sharp & Dohme
Evdokia Korakianiti, EMEA

Case Study Summary

Drug Substance Process Development

- Use of DOE in individual process steps yield different results, resulting in different types of correlations
  - Predictive models covering total ‘knowledge space’
  - Simpler statistical correlations covering only DOE space
- Use of standard processing platforms allows effective scale-up
  - From pilot scale (90kg) to production scale (several hundred kg) with good predictability
- Good understanding of factors controlling psd
  - Assures key factor for drug product process is in control

Case Study Summary

Drug Product Process Development

- Risk assessment led to use of large DOE at pilot scale
  - Full scale experiments to confirm DOE results but not to fully re-establish design space
- Significant use of PAT during development, technology transfer and in commercial process
- Particular focus on understanding of dissolution behavior vs. Bioavailability
  - Detailed analysis of dissolution steps
  - Disintegration rate predicts dissolution measurements

Case Study Summary

Control Strategy

Drug Substance

- Control strategy uses conventional approaches
- Control of attribute particle size distribution is linked to drug product design space

Drug Product

- Control strategy is using processing parameters as “knobs” but monitors material attributes as output
- Real-time release testing strategy

Main Topics Discussed

- Risk Assessment
  - A summary of the potentially relevant process parameters based on previous knowledge can be presented in a fishbone diagram.
  - Based on this fishbone diagram, each variable can be assessed in detail by a FMEA procedure and a Risk Priority Number (RPN) number is assigned. (RPN= impact (I) x probability (P) x detectability (D)).
  - It is recommended to include an explanation of how the scoring has been performed
  - It is recommeded to include a justification for the selection of variables for further study.

Common Understanding

- Design Space
  - DOE useful tool in development of a DS but not the only one
    - 1st Principles models
  - DS may cover one, or multiple unit operation(needs to be clear in the dossier)
    - Not all unit operations must have a DS
    - Unit operations without a DS will obviously not achieve the regulatory benefits (ie, ability to move within DS)

Common Understanding

- DS scale up
  - DS is usually developed at lab scale
  - There is no need to perform full DOEs at full scale to confirm the DS at full scale.
  - Good understanding of scale up phenomena is needed, some parameters may be scale independent (needs to be justified)
  - Scale up factors could be used to reduce concern about moving within DS at scale
    - Experiments within the DS at full scale could also be used to reduce the same concern.
    - Another option is have additional monitoring controls applied when there is a change within the DS to ensure that the DS is still valid and then relaxation to a less stringent control strategy.

Common Understanding

- DS needs to be complemented by an appropriate control strategy
- Critical process parameters remain critical even if controlled,
- CQAs: appropriate specs need to be set, even if not tested routinely
- Release based on CQAs and control of process parameters is possible if satisfactorily demonstrated (e.g. dissolution release based on particle size control, and disintegration test)

Areas For Further Work

- Level of risk assessment detail in the submission
- Description of non-critical parameters and impact on post approval changes
  - included in DS?
    - not described at all in submission
    - ranges established, but not part of design space?
- DS changes post approval
  - Changes to an approved DS are subject to the variations regulation in force at the time of the application
  - Post approval change management plans subject to discussion at the moment; outcome still to be seen
  - DS is not set in stone
- **DS is expected to change / improve as experience is gathered**
  - **How to achieve this is subject for future discussion**

Areas For Further Work

- Acceptance criteria for large sample sizes (EDQM ongoing work)
- Draft NIR guidance
- And much more….