Regulators Perspective on Quality by Design

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Pharmaceutical Development

- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
- Quality by design (Q8R): New Paradigm
  - A more systematic approach to development may include, for example, incorporation of *prior knowledge*, results of experimental studies using *design of experiments or multivariate data analysis*, establishment of a control strategy, *use of quality risk management*, and *use of knowledge management* (see ICH Q10) throughout the *lifecycle* of the product.
- Pharmaceutical Development is a dynamic, not a static process: lifecycle, continual improvement

Quality Target Product Profile

- Intended use in clinical setting, route of administration, dosage form, delivery systems
- Dosage strength(s)
- Container closure system
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product

Q8 Additional Opportunities

- Depending on the level of development (scientific understanding), opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:
  - risk-based regulatory decisions (reviews and inspections);
  - manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
  - reduction of post-approval submissions;
  - real-time quality control, leading to a reduction of end-product release testing.

New Paradigm

- Main message:

  Development is no more isolated and is living across the lifecycle of the product/process within a Quality Management System
- The new Paradigm to Quality is based on science, risk management tools and the establishment of an efficient Quality System.
- An integration of these three elements should enhance the process for ensuring quality and facilitate continual improvement.
- Use of risk management tools enhance the transparency of the development strategy of a medicinal product.

Pharmaceutical Development (QbD): *Demystification*

- A systematic approach will facilitate the process to achieve quality and should automatically generate more knowledge.
- Not necessarily new requirements:
  - Pharmaceutical development has anyhow to be done
  - QbD does **not** require the establishment of e.g., design space or real time release testing: a company might decide based on full scientific understanding not to establish a design space or RTR testing.
  - The level of development will depend on the complexity of the process and product and on the opportunities chosen or wanted by the applicant.

Advantages of Enhanced Development

- More product and process understanding
  - Process control
  - Quality derived from process control
  - Design space
  - Real time release
- Away from 3 validation batches
- Less batch failure
- More confidence from the Regulators
- ……..

Examples of Poor Development ?

- Development
  - appearance of a new polymorphic form on a marketed product; influence on in vitro dissolution rate: influence on bioavailability?
- Manufacturing process: scaling up
  - 2 products not marketed: manufacturer was unable to manufacture production scale size batches
- 3 variants of a medicinal product were not bioequivalent

  (combination of pilot scale and commercial scale batches (drug substance/drug product)).

Activities in EU

- Activities within Quality Working Party
  - Scientific advice
- Joint meetings QWP and GMP/GDP IWG
- Activities within the PAT Team:
  - Joint QWP, BWP, GMP/GDP IWG
  - Advice to Industry
  - Publication of Q&As
  - Training
- Participation at ICH activities (IWG Q8, 9, 10)

Some Considerations

- The quality of medicines is determined by their:
  - design, development, in process controls, GMP controls, process validation, specifications,……
- It is up to the manufacturer to develop a product fit for use
- It is up to the assessor to evaluate if the product is suitable for its intended purpose.
- The level of development will depend on the complexity of the process and product and on the opportunities chosen or wanted by the applicant (strategic decision of a company)
- An introduction in the application file explaining the rationale behind the development strategy, including the overall control strategy, for this particular product is highly welcome.
- Use agreed terminology

Some Considerations (2)

- QbD covers both development and control strategy
- Prior knowledge
- Acceptance criteria: end product testing versus RTRT
- Knowledge Management
- Knowledge versus data:
  - Data on site: what does that mean?
- Design Space and Proven Acceptable Ranges: (see also ICH IWG Q8, 9 and 10 Q&As).
- RTRT and batch release should not be confused (see also ICH Q&As on Implementation Q8, 9, 10)

Some Considerations (3)

Consequence on the Evaluation of Dossiers for Submission for MA

- Science based application files
- Change in review process
  - Enhanced collaboration between assessors and inspectors already at time of submission and during life cycle of the product
  - Clarification of respective responsibilities
- Pre-approval inspection:
  - Joint inspector/ assessor (case by case basis)

Quality by Design is not a slogan

Don’t claim it , do it

Thank You for Your Attention