Agence nationale de sécurité du médicament et des produits de santé

Workshop on process validation

General concepts on process validation

Kowid Ho

Scope / background

- Process evaluation/validation of biotechnology derived proteins used as active substance in the manufacture of medicinal products (i.e. scope of Q6B)
- Address data requirement for process validation/evaluation for submission of a marketing authorisation application or variation.
- Process Validation can be based on a traditional or enhanced approach to process development.
  - Traditional and enhanced approaches are not mutually exclusive.
  - A company can use either a traditional approach or an enhanced approach to process validation, or a combination of both.

Process development

- Not considered as part of process /validation
- But:
  - Comprises an essential prerequisite in defining the criteria and conditions to be addressed in process validation studies.
  - Should identify which ***material attributes*** *(e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates)* and ***process parameters*** that should be further evaluated during process evaluation/validation studies.
  - Risk assessment including documented prior knowledge should be used to identify and justify the material attributes and process parameters with the potential for having an effect on drug substance CQAs and/or process performance.
  - Preliminary acceptance criteria or limits should be defined

- *Difference with "process characterisation"?*

Process validation (ICHQ11)

- *Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes.*

- *Process validation can include the collection and evaluation of data, from the process design stage throughout production, that establish scientific evidence that a process is **capable of consistently delivering a quality drug substance**.*

Process validation

- Normally include **evaluation** and **verification** of process steps and the complete process

- Evaluation and verification activities: **often confounded in a same study**; not always necessary to make a difference between these activities as long as the evidences required for their demonstration are appropriately presented.

- ***Controls*** *(e.g. quality attribute, performance indicator, process parameter, controls implicit in the design of the process):* normally go beyond the routine control system performed during routine production.

- *What is the Industry understanding of process performance indicators/parameters for the upstream and downstream processes? Would these terms differ from consistency indicators/parameters?*

Process validation

- Data collected from studies representative of the final commercial process
- Contribution of data from small-scale studies to the overall validation package will depend upon demonstration that the small-scale model is an appropriate representation of the proposed commercial scale
- Data derived from commercial-scale batches should confirm results obtained from small scale studies used to generate data in support of process validation.
- Where appropriate, prior knowledge could be used to support some claims

Process evaluation

- Process evaluation studies:
  - should provide evidence that, when operating in accordance with conditions described in process description, the complete manufacturing process and each step/operating unit have been appropriately designed to obtain a product of the intended quality.
  - should include
    - the evaluation of the ability of each step to obtain output of desired quality at small and/or full scale as appropriate.
    - the results, demonstrating that when operating in accordance with the defined controls for material attributes and process parameters, the process is able to deliver quality attributes and process performance results in compliance with their pre-defined ranges, should be presented.

Process evaluation

- Where appropriate, evaluation of selected step(s) operating in worst case and/or abnormal conditions (e.g. cumulative hold time, spiking challenge) could be performed to support or demonstrate the robustness and the capability of the process to deliver product of the intended quality in these conditions.

- In some cases, these activities could be built into process verification studies.

- Depending on the level of evidence provided to demonstrate the high performance of the step(s) and the relevance of experimental model with regards to the final process, these studies could leverage data requirements for process verification (e.g. reduced number of batches) and/or control strategy (e.g. alternative approach to end product testing).

- *Process evaluation: main data to support PAR?*

Process verification

- Process verification studies should ***confirm*** that the final manufacturing process (i.e. full scale commercial process) performs effectively and is able to produce a drug substance or intermediate meeting its predetermined controls and acceptance criteria.

- Process verification data (e.g. process step results, batch analyses) should be presented in the MAA on an appropriate number of batches (to confirm consistency) produced with the commercial process and scale

- Process verification studies should ***normally be completed and included in the Marketing Authorisation Application***. In some circumstances, concurrent validation could exceptionally be considered.

- As an alternative approach, ***continuous process verification*** could facilitate registration of concurrent validation studies and/or manufacturing process changes throughout the remainder of the product lifecycle.

- *Process verification: main data to set Normal Operating Ranges?*

Process validation

- *For process evaluation and verification, is it necessary to have a higher level and frequency of sampling and testing as compared to routine manufacture?*
- *Would you present this data in the dossier?*

Continued process verification

- Subsequent to successful process validation activities for MAA
- Monitor product quality and process performance to ensure that a state of control is maintained throughout the commercial part of the product lifecycle.
- To be performed in compliance with EU GMP
- *Presentation of continued process verification program in MAA to support process validation?*
- *Include extended control system performed at appropriate frequency, in accordance to internal limits ? acceptance limits ?*
- *Include protocols covering aspects that will be verified on an ongoing basis? Periodicity?*

Continued vs Continuous Process Verification

- **ICH Q8:**
  - Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

- **Merriam-Webster:**
  - *Continuous*:
    - marked by uninterrupted extension in space, time, or sequence
  - *Continued*:
    - lasting or extending without interruption
    - resumed after interruption
  - *Continuously*: continuing without stopping **:** happening or existing without a break or interruption

Continued vs Continuous Process Verification

- **ICH IWG PtC:**
  - CPV can be applied to an entire process, or to portions of a process, together with traditional process validation approaches.
  - Generally, for initial process validation, CPV is more appropriate when an enhanced development approach has been applied. However, it can also be used when extensive process knowledge has been gained through commercial manufacturing experience

- **QWP draft guideline on process validation** (29/03/2012):
  - CPV: Risk based, real time approach to verify…

Continued vs Continuous Process Verification

- **QWP draft guideline on process validation** (29/03/2012):
  - *Continued Process validation*: documented evidence that the process remains in state of control during commercial manufacture

- **ICH Q11:**
  - The development and improvement of a drug substance manufacturing process usually continues over its lifecycle. Manufacturing process performance, including the effectiveness of the control strategy, should be periodically evaluated.

- **ICH Q7:**
  - Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner.

Continued vs Continuous Process Verification

	Continous Process Verification	Continued (/ongoing?) Process Verification
Aim	- Initial demonstration and/or maintenance of a state of control	- maintenance of a state of control
Frequency	- uninterrupted - timely manner	- resumed after interruption - periodic
Testing/Monitoring	- Not limited to CPP and CQA - Include process performance	
Enabler	- PAT tools (MSPC, in-line control…) - Extensive process knowledge and understanding	- GMP compliance - Control strategy during product lifecycle (ex. design space verification)

MANUFACTURING PROCESS DEVELOPMENT, EVALUATION & VALIDATION