Process validation and adaptive pathways

With specific attention to continuous process verification

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Disclaimer: Personal views only, meant to initiate further discussion. Does not necessarily reflect current or future view of MEB, EMA, CHMP, or other regulator body
A note on terminology

- Terminology matters!
- Clear/unequivocal terminology necessary
- However, (discussions on) terminology should support instead of distract from scientific issues
Adaptive pathways

- MEB committed to improving access to innovative medicines
- Staggered approval(?)
How do patients get access to a new drug?

CTs
Individual use
Registry
PAES
PASS
Prescription

Knowledge

TODAY

Time / Phase of development

I  II  III  IV

Modified after T. Salmonson (CHMP)
How do patients get access to a new drug?
How do patients get access to a new drug?

Knowledge

CTs
Individual use
Registry
PAES
PASS
prescription

BY ADAPTIVE LICENSING

Time / Phase of development
How do patients get access to a new drug?

Knowledge

CTs
Individual use
Registry
PAES
PASS
prescription

1st Approval

BY ADAPTIVE LICENSING

Time / Phase of development

I
II
III
IV
How do patients get access to a new drug?

1st Approval
2nd Approval

BY ADAPTIVE LICENSING

Time / Phase of development

CTs
Individual use
Registry
PAES
PASS
prescription
Place of verification(?)
‘Normal’ verification

- Process verification studies should confirm that the final manufacturing process (i.e. commercial scale process) performs effectively and is able to produce an active substance or intermediate of desired quality. Such studies are generally performed in accordance with normal set points for operating conditions and process parameters.
- Process verification data (including process step results and batch analyses) should normally be completed and presented in the regulatory submission using an appropriate number of consecutive batches produced with the commercial process...
  - ‘Proof of the pudding...’
Continuous process verification

- **Definition (ICH Q8)**
  - *An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.*

- **Description (cf. EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1)**
  - Principles consistent between BWP and QWP guideline;
  - taking into account different general validation requirements for biologicals and small molecules.
Continuous process verification (ctd.)

- Continuous process verification in which manufacturing process performance is continuously monitored and evaluated is an alternative approach to traditional process verification. Making use of this approach could facilitate acceptance of fewer batches in the verification studies.
Continuous process verification (ctd.)

• (..) a science and risk-based real-time approach to verify and demonstrate that a process that operates within the predefined specified parameters consistently produces material which meets all its CQAs and control strategy requirements. In order to enable continuous process verification, companies should perform, as relevant, extensive in-line, on-line or at-line controls and monitor process performance and product quality on each batch. Relevant data on quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end points, and assessment of CQA and critical process parameter (CPP) trends.
Continuous process verification (ctd.)

- Feasible for biologicals (PAT tools available?)
  - Intra-batch consistency and scale dependent effects addressed?
- Pre-approval, post-approval, or both?
- Limited in time or truly ‘continuous’?
  - Life cycle management of associated CPPs and IPCs?
- Regulatory experience ‘limited’.
Continued (‘ongoing’) process verification

- **Post-approval**
- **GL:** There may be cases where it will not be possible to present full validation data at the time of the regulatory submission and the process requires further verification.
  - E.g. niche products; accelerated programs for unmet medical need.
- **In these cases, dossier should contain how the data generated through such verification activities will be managed to facilitate the acceptance of the claimed process step.**
  - E.g. a protocol.
- **This option should only be used when common validation studies are not possible and it is therefore expected to be a rare event.**
Concurrent validation (‘/verification’)

- **Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches (GMP Annex 15).**
  - Could be considered under exceptional circumstances (e.g. urgent medical need),
  - Evidence should be provided to demonstrate i) that studies performed for process evaluation are appropriate representations of the commercial process, and ii) that control strategy will properly verify that the process has performed as intended and that active substance and intermediates comply with pre-defined acceptance criteria.
Concurrent validation (`/verification’)

- Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches (GMP Annex 15).
- Concurrent validation may be based on traditional validation approach (no CPV, no PAT).
- Intra-batch consistency and scale dependent effects addressed?
Possible non-alignment with other approaches

- No verification (batches) at time of MAA implies:
  - Development not yet finalised
    - Accelerated assessment procedure: Mature dossier (no MOs)
    - Comparability during development: No scale-up or already addressed.
      - Verification batches really only confirmatory?
      - Post-approval scale up (adaptive path)
    - Certain ICH Q12 enablers may require mature dossier to meet full potential
      - Established conditions not yet firmly established(?)
Conclusion

- Adaptive pathways actively being scouted
- Continuous Process Verification remains a ‘new’ concept and little experience has been collected.
- Any form of Continuous Process Verification will depend heavily on extensive monitoring (PAT etc.)
- Door is open for alternatives to ‘standard’ process validation/verification
  - Niche products/highly unmet medical need