EMA Expert Workshop on Validation of Manufacturing for Biological Medicinal Products

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Traditional Validation - Downstream

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Content of the Presentation

5. Should qualification and variability of biological raw materials and other materials (e.g. chromatographic resins) be addressed in the process validation guideline? If yes, what should be included?

7. What are Industry views on the information to be documented in the dossier in relation to reprocessing? Is it always restricted to an exceptional event (e.g. mechanical failure of equipment)?

8. For process evaluation and verification studies, 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?

10. How to demonstrate validation of adaptive processes (e.g. with feed forward/feed back loops?

\+ Other topics from the abstract

5. Should qualification and variability of biological raw materials and other materials (e.g. chromatographic resins) be addressed in the process validation guideline? If yes, what should be included?

- A risk based approach should be used
  - If the variability of the material is determined to be a critical process input (impact on CQA), which cannot be adequately controlled, e.g. by material income testing, it should be investigated during PV.
  - If not, variation of batches during PV should not be required.

- Materials should be assessed for potential variability
  - For materials, unlikely to vary significantly (e.g. Protein A Sepharose), the use of one resin batch for PV is considered to be sufficient
  - Prior knowledge, e.g. use of the same resin for other processes, should be considered.
  - Vendor qualification, vendor testing/certificates and material income testing can also be used to ensure consistent material properties.

5. Should qualification and variability of biological raw materials and other materials (e.g. chromatographic resins) be addressed in the process validation guideline? If yes, what should be included?

- Characterisation studies
  - In order to provide additional assurance, different batches of materials can be evaluated during development at small scale
    - E.g. source batches with properties that are spread across the range controlled by the resin manufacturer's own range (e.g. ionic capacities; particle size distribution; affinity ligand density etc…)
- Manufacturing experience
  - Potential variability of different batches should be controlled during commercial manufacturing, e.g. as part of continued process verification.

5. Should qualification and variability of biological raw materials and other materials (e.g. chromatographic resins) be addressed in the process validation guideline? If yes, what should be included?

Resin reuse

- Usually the number of resin re-use cycles is established through prospective small-scale validation studies
- Resin performance is confirmed at manufacturing scale during process verification (for a limited number of cycles)
- Typically resin performance testing is continued post process verification under a validation protocol, until the maximum number of cycles is reached.
- In the dossier, data from small scale re-use studies and commercial scale process verification should be included.
- Further commercial scale data for resin re-use should be addressed by the companies continued verification program and not be part of the dossier.

8. For process evaluation and verification studies, 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?

- The testing (sampling, frequency, tests) for process validation as well as for continued process verification should be defined as part of the overall control strategy considering
  - complexity of the process
  - level of process variability
  - available process understanding (e.g. development data)
- Depending on the level of process and product understanding, a science- and risk-based testing strategy within the overall control strategy will allow for meaningful and efficient control
  - The better the process and product understanding in combination with low process variability → the less additional testing necessary during process validation (could result in no additional testing / sampling at all)
  - Less process and product understanding in combination with high process variability → higher level and frequency of testing which might continue into commercial manufacturing until process can be concluded to be statistically under control and capable

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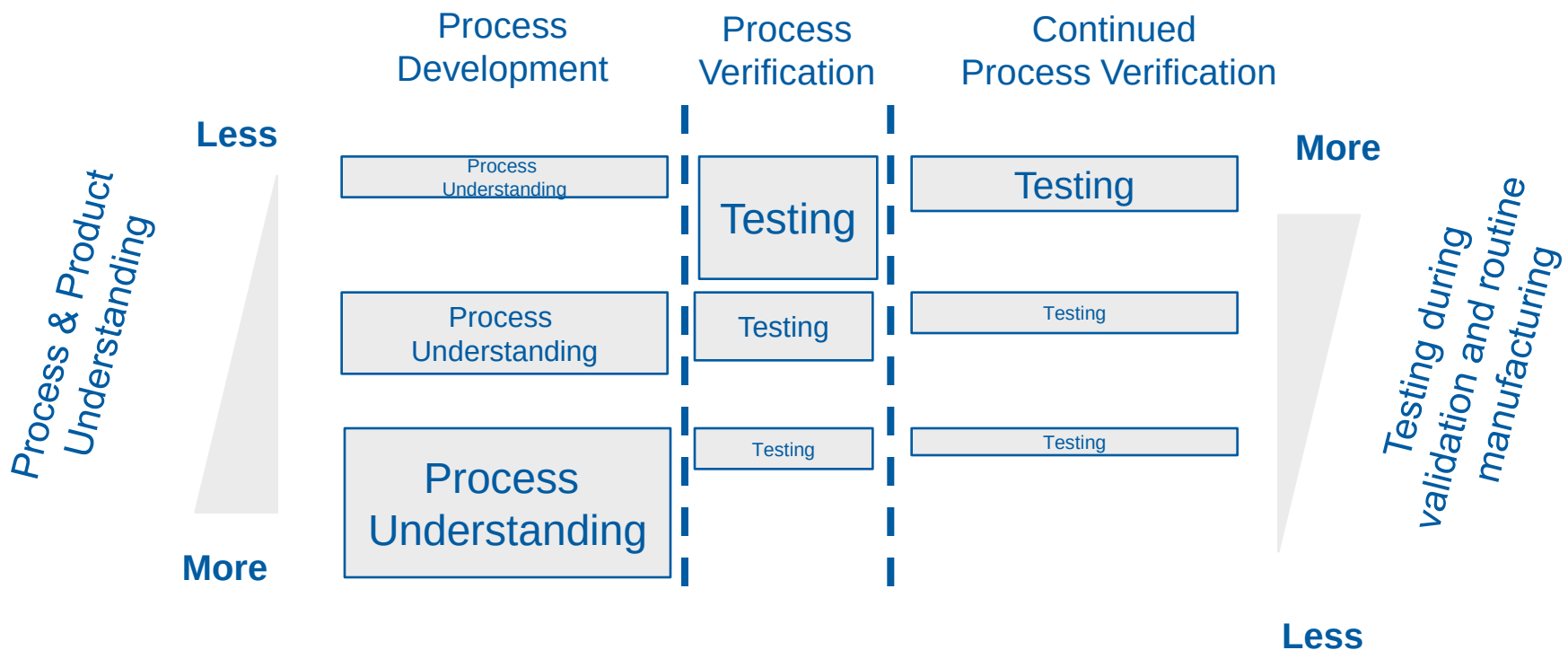

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- Sampling plans should be based on statistical rationales, as applicable
- Statistically based sampling plans may not be useful for processes or unit operations that yield a single homogenous pool of material
- Data from additional sampling and testing should be in the dossier
  - if necessary to conclude about process validation, considering demonstration of control and consistency
- Analytical methods for commercial batch release require validation according to ICH Q2(R1)
- Analytical methods used for further characterization of the process (during process verification and continued process verification), with potentially new analytical methodology, should be demonstrated to be fit for purpose, but not necessarily fully validated (scientifically sound, e.g. specific, sensitive and accurate)
- Continued process verification should not be part of the dossier to allow flexibility for modifications throughout the program. The continued verification program and data should be subject to inspection.
- The use of continued verification data for continuous process improvement should be clarified

7. What are Industry views on the information to be documented in the dossier in relation to reprocessing? Is it always restricted to an exceptional event (e.g. mechanical failure of equipment)?

Definitions ICH Q7A

- **Reprocessing**
- **Introducing an intermediate or API**, including one that does not conform to standards or specifications, **back into the process and repeating** a crystallization step or other
- appropriate chemical or physical manipulation steps (e.g., distillation, filtration,
- chromatography, milling) **that are part of the established manufacturing process.**
- Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

- **Reworking**
- **Subjecting an intermediate or API** that does not conform to standards or specifications **to one or more processing steps that are different from the established manufacturing process** to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

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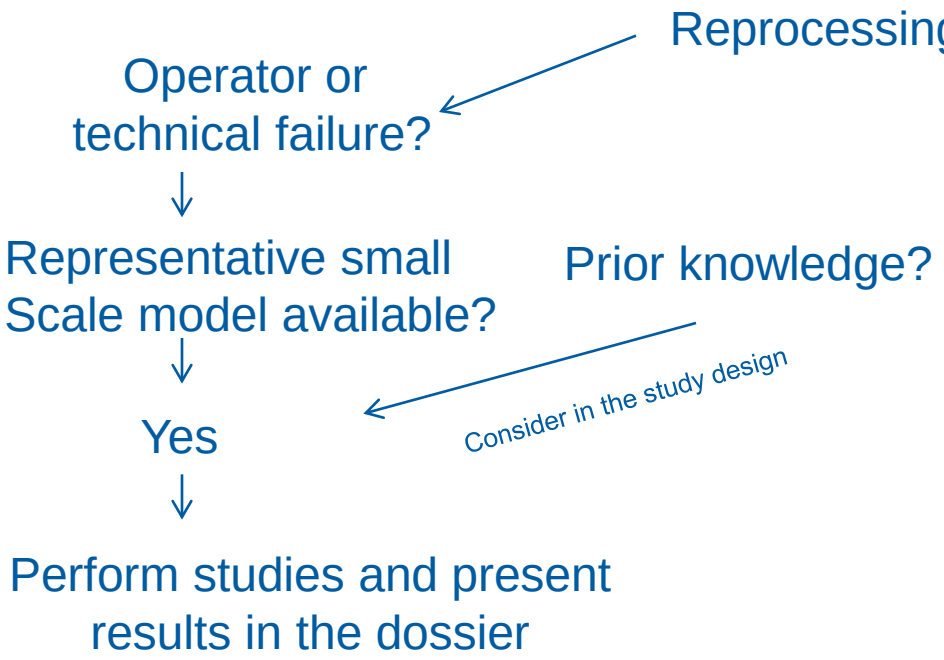

Discussion:
If a validated process delivers an unexpected result, this is an indicator of a lack of process understanding and control. Typically this can not be foreseen and requires a deeper investigation and an update of the process controls. Pre-approval in the dossier is problematic.

Discussion:
If a validated process delivers a non-conformance, e.g. a filter integrity test failure, due to reasons that are not indicative for a lack of process understanding or control, this can typically be foreseen and be supported by, e.g. re-filtration studies. Pre-approval in the dossier would be preferable.

7. What are Industry views on the information to be documented in the dossier in relation to reprocessing? Is it always restricted to an exceptional event (e.g. mechanical failure of equipment)?

Examples

- Repetition of a filtration step
  - Typically multiple filtrations are performed routinely in downstream
  - Data from process validation show that filtration does not have an impact on product quality by pre/post filtration testing
  - Small scale models for filtration studies available (e.g. bacterial retention studies)
  - Small scale studies for multiple re-filtrations can be provided in the dossier
    - Note: Maximum validated hold times must not be exceeded
- Re-concentration after over-dilution of a UF intermediate
  - After UF intermediates are typically adjusted to a target concentration
  - If dilution overshoot, the intermediate can not be further processed
  - Introducing the intermediate back to the UF system and to concentrate again is a repetition of the same step
  - Data can be generated during process validation and be provided in the dossier
    - Note: Maximum validated hold times must not be exceeded

10. How to demonstrate validation of adaptive processes (e.g. with feed forward/feed back loops?

- Feed back loops are in use since a long time to operate equipment
- Adaptive processing allows the real time linkage of process parameters and quality attributes through live feed-forward or feed-back control
- The ultimate aim of adaptive processing is to move away from reliance on “off-line” testing of discrete samples for product quality characteristics, and the inherent associated time delays
- Adaptive processing requires a deep understanding of the relationship between process parameters and product quality attributes
- Elements of process analytical technology and informatics will facilitate adaptive processing

Other Topics from the Abstract

Hold times

- Purpose is to investigate product quality over a pre-defined time period under defined conditions, e.g. temperature, container etc.
- Hold time studies can have a different scope:
  - Long time storage of process intermediates
  - Short time storage between process steps
- Often, storage of intermediates is impractical at commercial scale
  - Typically stability indicating tests are done at small scale
  - Bioburden testing at small scale does not represent the commercial equipment. Bioburden control should be demonstrated by other means, e.g.
    - By routine bioburden testing of samples pre-filtration in the commercial facility combined with validation studies demonstrating effective filtration and container sterilization. In this scenario routine bioburden testing post storage can be eliminated.
    - By routine bioburden testing at the end of the actual hold time.

Other Topics from the Abstract

- Depending on the scope it can make sense to do cumulative studies or not, e.g.
  - If a final drug substance bulk can be stored for more than just weeks, the impact on drug product stability should be assessed.
  - If a final drug substance can be stored for extended (longer) time periods, a prospective cumulative study may be unreasonable, because it may take years.
  - Short time storage between process steps are typically used to allow for production flexibility (e.g. shift work). Storage of intermediates between process steps for the maximum allowable time typically does not occur. Thus cumulative studies do not add value for the commercial process.

Hold time data in the dossier

- Usually hold conditions and time and the resulting product quality data / acceptance criteria from the stability indicating assays are filed.
  - Due to the reasons described on the previous page, bioburden data from small scale studies

- In case of hold time changes, it would be preferable to describe the hold validation program including acceptance criteria in the dossier to reduce efforts for reviewer and industry.

Other Topics from the Abstract

Pooling of intermediates:

- Pooling of different intermediates is often done in downstream processing, e.g. to for final intermediates to achieve the batch size needed for filling
  - All intermediates have to be of the specified quality
  - Homogeneity should be ensured by mixing studies
  - If mixing is associated with filtration, supporting data may be needed

Pooling data in the dossier

- It would be preferable to describe the option for pooling in the dossier, including:
  - the prerequisites described above
  - reference to associated studies, such as mixing or multiple filtrations

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