Agence nationale de sécurité du médicament et des produits de santé

Workshop on process validation

Session 1(b): Traditional approach - Downstream process

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Purification

- **Evaluation**:
  - Capacity of the purification procedures to obtain the desired product and to remove product and process-related impurities (e.g. unwanted variants, host cell derived proteins, nucleic acids, carbohydrates, viruses).
  - Quality of process intermediates (i.e. appropriate purity/impurity profile for the given stage)
  - Requires adequate analytical methods
  - For selected step(s):
    - e.g. steps for which high impurity or viral clearance are claimed
    - operating in worst case and/or abnormal conditions (e.g. cumulated hold times, spiking challenge) performed to document the robustness

Purification

- **Evaluation**:
  - Depending on the level of evidence provided: could leverage some process validation and/or control strategy data requirements.
  - Process conditions (e.g. column loading capacity, column regeneration and sanitisation, flow rate, length) should be appropriately evaluated.
  - Performance parameters/indicators (e.g. yield, chromatographic profiles)
  - Pooling strategy and impact on drug substance consistency
  - Columns life time:
    - Demonstration of appropriate performance and integrity (e.g. clearance, collection of intended variants, leaching).
    - small scale studies: appropriate to estimate and set the maximum number of cycles at the time of MAA,
  - Hold times
  - Reprocessing

Purification

- **Verification**:
  - Quality of process intermediates (i.e. appropriate purity/impurity profile for the given stage)
  - Process parameters and Performance indicators in accordance to proven acceptable ranges

- **Continued Verification could include:**
  - *Control of performance and integrity of operating units (e.g. purification column) ?*
  - *Running period and periodic control of quality attribute(s) for which RTRT is done ?*
  - *Cumulative studies ?*
  - *Reprocessing?*

Reprocessing

- Reprocessing: introduced back into the process by repeating a step (e.g. filtration) that is part of the established manufacturing procedure.
  - Limited to occasional process excursions.
  - The reason of the failure should be understood and should not impair the quality of the product.
  - Could be allowed only under appropriately defined conditions.
  - Should be described in the MAA.
  - Validation data expected, demonstrating that the reprocessing step(s) do not impact the quality of the active substance.

- *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)?*