Agence nationale de sécurité du médicament et des produits de santé

Workshop on process validation

Closing remarks

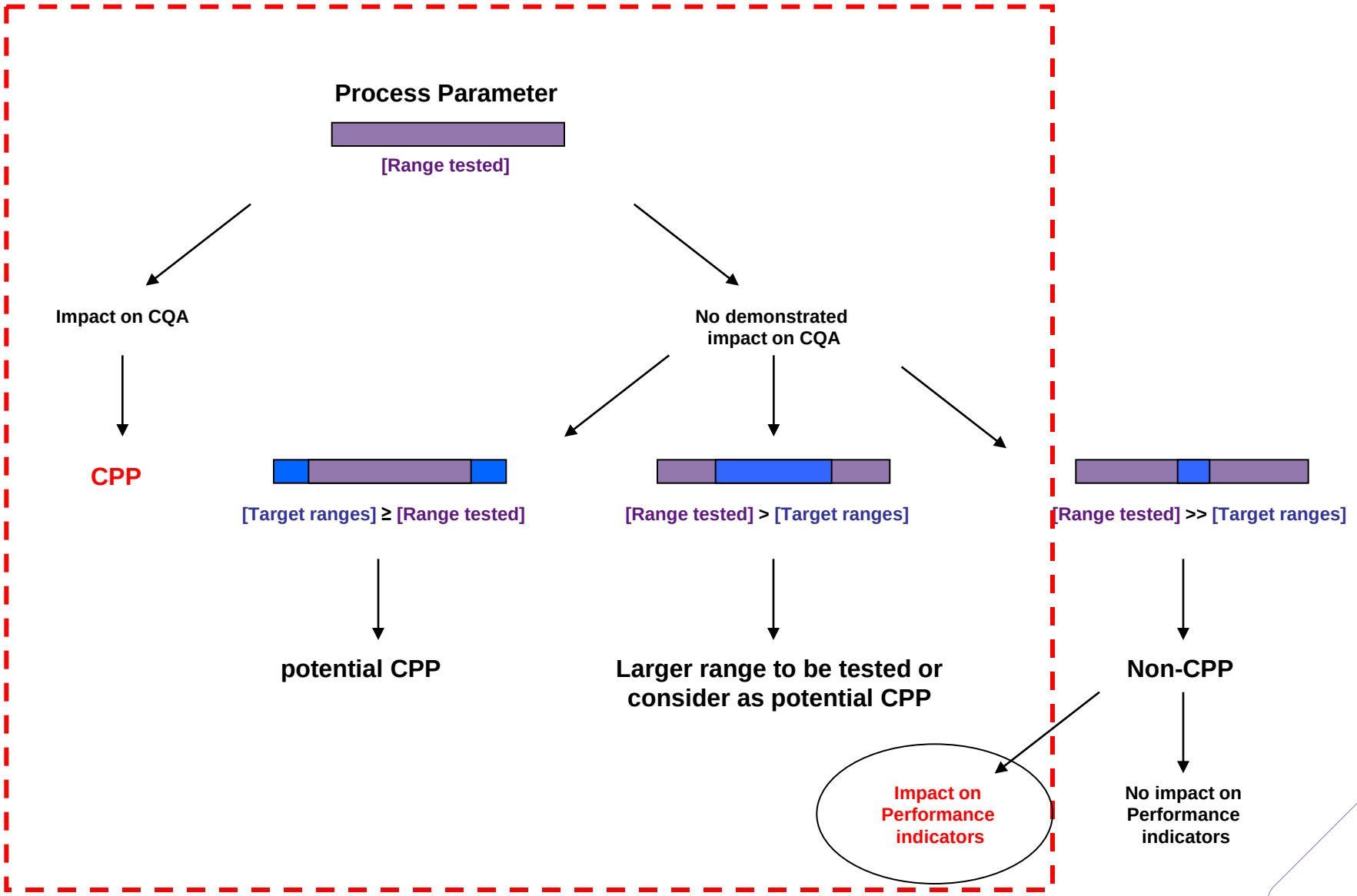
Kowid Ho

Process validation biotech drug substance General concepts

- **Objective**:
  - To establish scientific evidence that a process is capable of consistently delivering a quality drug substance.
  - Will justify the manufacturing process described in S2.2
  - More consistent data submitted and assessed
- **Data expected:**
  - Process evaluation (small and/or full scale)
  - Process verification (full scale) or continous process verification
  - +/- Continued process verification

Process validation biotech drug substance General concepts

- Issue with terminology
  - Process
    - Characterisation: to design intended process
    - Evaluation: for the process representative of final process
    - Verification: full scale +/- at target
    - Continued Verification
  - Process PERFORMANCE indicators/parameters vs CONSISTENCY indicators vs KEY PERFORMANCE indicators
    - Differenciation between input and output?
    - Process performance indicators and parameters that don't impact CQA's do not need to be included as regulatory commitments in the MAA?
    - Point that will require further discussion…



Expected to be included in process validation studies

Process validation biotech drug substance
General concepts

- Justification of PAR
  - Mainly based from evaluation data?
  - Excursion from PAR: GMP issue?

- Justification of NOR
  - Mainly based from verification data?

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 - Lifecycle management
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)
MAA Submission	- Included in the MAA	- Prospective proposal - May be described in MAA

Process validation biotech drug substance General concepts

- Non-CPP measures included:
  - Markers of process consistency
  - Only if non redundant or indicator status?
- Material and intermediate attributes linked to CQA outcomes
- Indirect or indicator parameter or attributes demonstrating drift or loss of control
  - Multi-signal/multi-parameter probes
  - Shear forces, gas exchange rates, column-ligand density, non-critical attribute abundance or quality

Upstream

- Genetic stability of the cell line
  - Done prior to validation
  - Already captured in Q5s

- Process parameters and quality attributes to be tested
  - Inputs: can be varied; eg Process parameters
  - Outputs
    - CQA
    - Performance indicators (cell density, viability)
    - Consistency indicator ?
    - “Indicator”: more appropriate for output?
  - Criticality continuum… where to draw the line?
    - Controlled within narrow range?
    - For early warning sign?

Upstream

- Multi-harvest approach
  - Strategy company dependent
  - Need to cover complete harvest
- Performance indicators for the validation of a continuous perfusion process
  - Indicators and QA not that different from discontinuous fermentation

Upstream & Downstream

- Qualification of biological raw materials and other raw materials
  - Difficult to incorporate different lots in to validations studies
  - Evaluation to be performed to analyze potential variability
  - Risk based approach
  - “Critical Raw Material” need to be identified?

- Test frequency
  - Depends on process and product understanding, overall control strategy…
  - Less understood : More testing
  - For non release assay: demonstrated fit for purpose

Upstream & Downstream

- Single use
  - Risk assessment
    - impact on performance and QA; eg could be handled as high risk raw material for upstream
    - attention on extrables/leachables
    - Quality of the bags (eg sterility of bags) covered by vendor qualification?
  - Same principles for downstream and upstream

Upstream & Downstream

- Multifacility
  - List of difference + justification
    - How far can be stretched? Difficult to draw the line
    - Purpose and outputs still the same?
  - Risk assessment on potential impact / comparability exercise
  - PV to be done

Upstream & Downstream

- Scale Down Models (SDM)
  - Incomplete representation but needed !
  - Description and justification of inputs, design and outputs
    - Can explore large ranges
  - Outputs:
    - Product quality attributes > Performance indicators > Other characteristics
    - SDM should match large scale at target
    - Statistical approach: difficult to conclude with limited number of full scale batches
  - Non-equivalence & offsets
    - "a question of confidence…“
    - Depend on the intended use
    - Ideal should include off-target; doable for downstream? Could be done for upstream?
    - Could be leverage by proper control strategy / continued PV

Downstream

- Reprocessing
  - Extraordinary
  - Reprocess step does not impact product quality
  - Root cause clearly identified and does not impact product quality
  - Mainly limited to re-filtration or re-concentration steps

- Adaptive process and feed back loops
  - No real example of product quality directly measured in the process; future?

Downstream

- Hold times:
  - Long vs short time storage
  - Often, storage of intermediates is impractical at small scale
  - Cumulative studies of DS bulk:
    - if stored > weeks; impact on DP stability to be assessed
    - If stored > months unreasonable, could take years
  - Intermediate hold
    - Cummulating unlikely; unreasonable?
    - Program to be included in Continued PV?

Downstream

- Pooling intermediate
  - Intemediate of specified quality
  - Homogeneity ensured by mixing studies
  - Option to be described in dossier

Enhanced/QbD approach

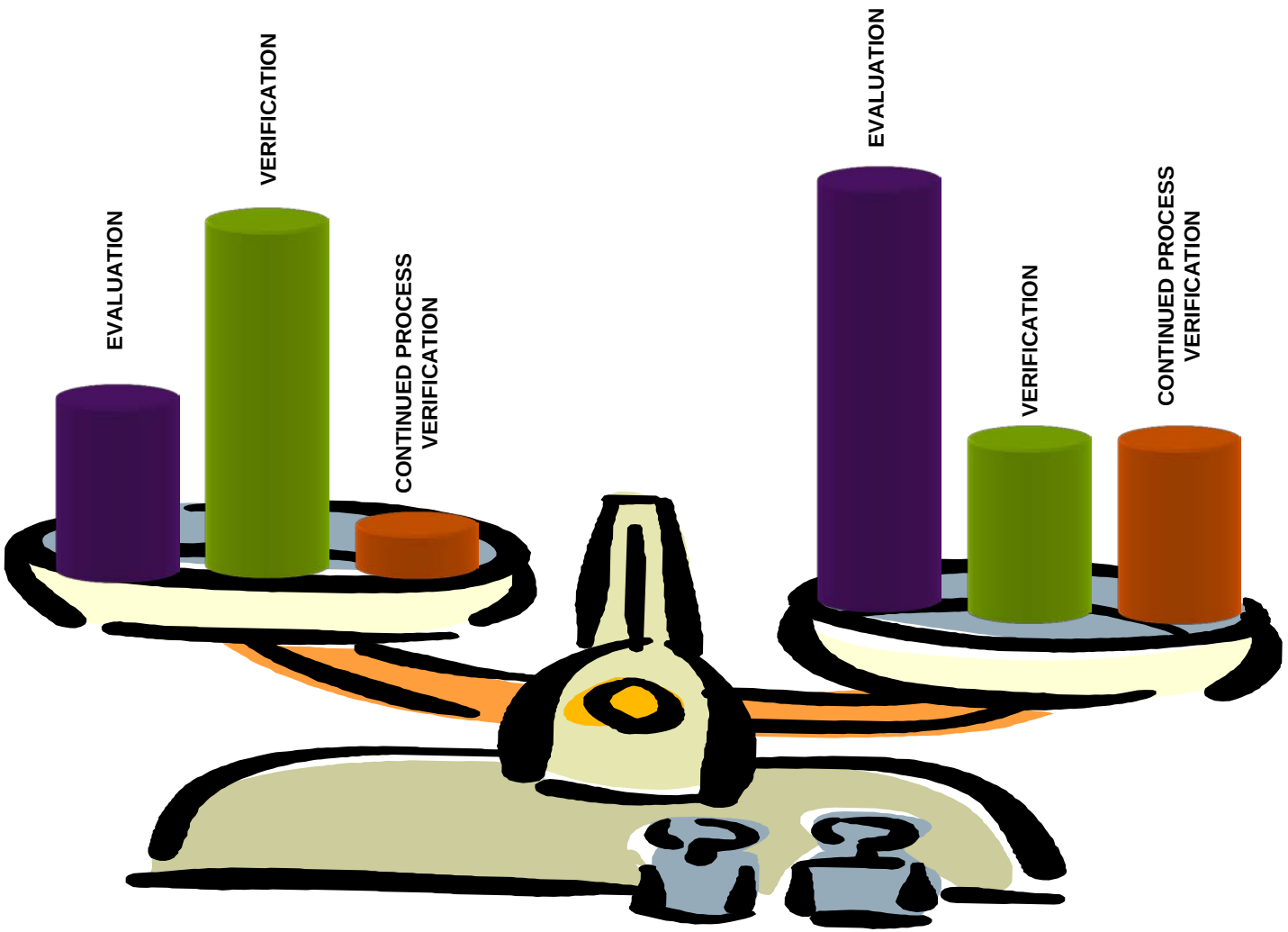
- Additional studies for enhanced approach
  - Mixture; PV approach likely to be a continuum from tradition to enhanced
  - More integrated approach
    - including Non-clinical and clinical aspects
    - Describe and manage influence of CPP on CQA
    - Control of materials (RM, intermediates…)
  - SDM

- Flexibility…
  - Considered as an OUTCOME rather than the AIM of enhanced approach for regulators
  - Also depends on data and knowledge shared

Data to be submitted in MAA

TRADITIONAL APPROACH

ENHANCED APPROACH



Closing remark

Continuous discussions…

to be continued…

Thanks you all !!!