EMA Expert Workshop on Validation of Manufacturing for Biological Medicinal Products

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Traditional Validation - Downstream

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Making Medicines Affordable

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The European Association for Bioindustries

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Topics of the Presentation

- What is the Industry understanding of "process performance indicators and parameters“ for the downstream processes? Are there any differences/similarity of this terminology compared with "material attributes", "consistency indicators/parameters"? Which indicators or parameters should be presented in the Marketing Authorisation. Application (MAA) to support process validation?

- In case of single-use equipments or facilities, what are the main differences between process validation studies and studies to qualify these equipments and facilities ?

- Multi-facility production:
  - What are the key elements in validation when a process gets transferred from one site (site 1) to another site (site 2).
  - How is a diversification of the product which might be caused by process changes at both sites during product life cycle time prevented. And how is comparability achieved and maintained?

- How to evaluate and verify reliability/predictability of small-scale models for the upstream and downstream processes?

Question 1

- What is the Industry understanding of "process performance indicators and parameters“ for the downstream processes? Are there any differences/similarity of this terminology compared with "material attributes", "consistency indicators/parameters"? Which indicators or parameters should be presented in the Marketing Authorisation. Application (MAA) to support process validation?

Traditional Downstream Process Validation
Parameter and Indicator - Process Parameter

- Defined during development and scale-up
  - Operation of Chromatography, membrane steps etc.,
  - Product stream conditions (pH, cond), if directly controlled
- Experiments are established to link process parameters, potential variability and product CQAs
- Control strategy has to be developed
- Process Parameters and associated control strategy, that impact CQAs are included in MAA
- Process performance indicators and parameters that don’t impact CQA’s do not need to be included as regulatory commitments in the MAA.

Traditional Downstream Process Validation
Parameter and Indicator - Process Performance Indicators

- Defined during development and scale-up
  - Example: Step yield and overall yield
  - Process performance indicators are not direct measures of product quality but are measures of process performance and consistency
  - DOEs are established to link process parameter with process performance indicators
  - Process performance and consistency also has a developed control strategy
- Process performance indicators and associated control strategy, that are important to understand process performance and consistency are described in MAA but are not considered as regulatory commitments. They are handled internally via the company quality systems.

Traditional Downstream Process Validation
Parameter and Indicator - Material Attributes

- Material attributes that are not part of the control strategy should not be submitted in the MAA but maintained under the review of the companies quality system
- Examples of controlled and non controlled material attributes
  - Pore size of a SEC → controlled
  - Ion binding capacity of a Ion Binder → not controlled

Question 2

- In case of single-use equipments or facilities, what are the main differences between process validation studies and studies to qualify these equipments and facilities ?

Traditional Downstream Process Validation
Single-use Equipment - Definitions

- *<Process Validation>* (ICH Q7A, D. Approaches to Process Validation)
  - Process validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

- *<Qualification> (ICH Q7A, C. Qualification)*
  - Before initiating process validation, appropriate qualification of critical equipment and ancillary systems should be completed

Traditional Downstream Process Validation
Single-use Equipment - Qualification and Validation

Qualification:

Finalize <qualification> working package acc. to ICH guideline (DQ, IQ, OQ, PQ)

→ Outcome of qualification effort is related to facility (stainless steel and/or disposable independent from any potential product

→ Qualification is a mandatory activity before starting PV

→ With no changes, qualification is a singular activity independent from number of processes to be validated

- <Equipment Qualification> is not considered to be part of the process validation package

Traditional Downstream Process Validation
Single-use Equipment - Qualification and Validation

Validation

Finalize <process validation> working package acc. to ICH guideline

→ Outcome is related to dedicated process in a qualified environment

→ Process parameter ranges have to be within the ranges defined and checked in equipment qualification
(e.g. flow of a pump in DSP, mixing speed etc.)

Obvious difference <stainless steel> vs. <single-use equipment>

→ No need for cleaning validation for <single-use equipment>

Traditional Downstream Process Validation:
Single-use Equipment - Leachables and Extractables

- Additional efforts to be considered in MAA using single-use equipment
  → Leachables/Extractables studies

- Elements in MAA
  - List of all disposable material used at different steps
  - Duration of product/intermediate contact with disposable material incl. worst case assumptions
  - Risk assessement regarding impact on quality target product profile
    - Detectability is low
    - Discriminate early stage and late stage process steps in purification

    → Impact on removability of leachables
  - Design and result of studies (final report)

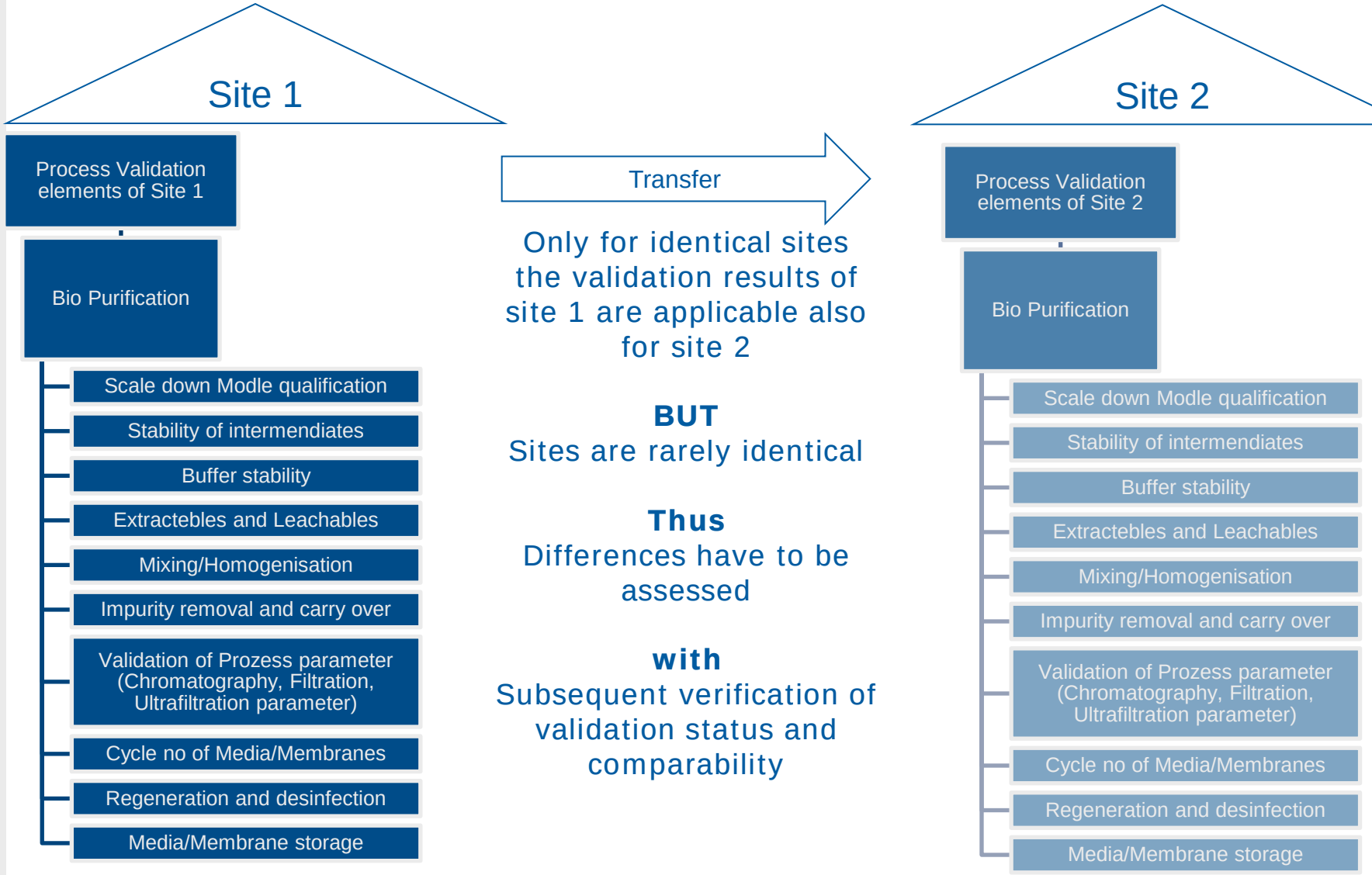
Question 3

- Multi-facility production:

What are the key elements in validation when a process gets transferred from one site (site 1) to another site (site 2). How is a diversification of the Processes prevented which might be caused by process changes at both sites during process life time. And how is comparability archived and maintained?

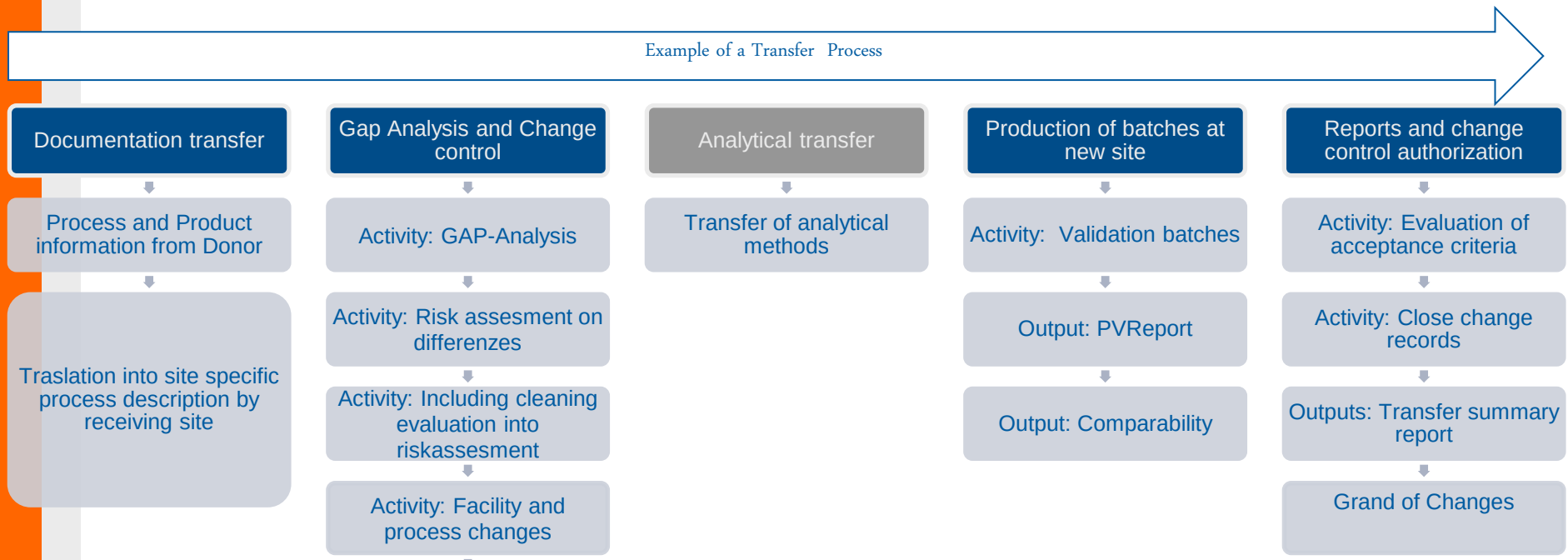
Traditional Downstream Process Validation

Process transfer – Elements and Principles



Traditional Downstream Process Validation

Example - Activities to Assess the *Differences during process transfer*



Examples on potential differences to be assessed:

- Membranes → Influence on product and small molecule removal
- Product concentration → Influence on product
- Pressures during filtration → Filter performance; Influence on Productquality

Traditional Downstream Process Validation
Multi-facility Production - Comparability and Diversification

- Comparabilty is shown by:
  - Meaningfull statistical methods
  - Extended Measurements during validation runs at site 2
    → Extend is case specific and depends on GAP analysis and risk assesment.
- Diversification by process changes can be prevented by:
  - Change management
  - Meaningfull specification of raw materials (material attributes) and raw material testing?
  - Continous and/or periodic (statistical found) process monitoring at each site

Question 4

- How to evaluate and verify reliability/predictability of small-scale models for the upstream and downstream processes?

  - Mainly adressed in the Upstream and the Advanced Process Validation presentations

  → Principles for small scale models with respect to the traditional approach are presented here

Traditional Downstream Process Validation
Small Scale Models

- Variety of applications for validation of down stream processes

- Evaluation of conditions that are difficult or impossible to be studied at manufacturing scale

Two types of Models

- Full: miniaturized versions of the manufacturing scale process (-step).

Example:

- Chromatography models employed under manufacturing target conditions

- Partial: aspects of the at scale system are modeled, typically to isolate or exaggerate a condition.

Example:

- Intermediate hold time study models – vessel surface area to volume ratio, temperature, and time may be exaggerated at small scale beyond the manufacturing conditions to evaluate a challenge condition

Traditional Downstream Process Validation

Applications of Small Scale Models

Purpose	Model	Type	Conditions
Viral clearance	Chromatography	Full model	Target
	Virus Filtration	Full model	Load challenge
	Low pH Inactivation	Partial model	pH and temperature challenge
DNA clearance	Chromatography	Full model	Target
Intermediate hold time	Product hold vessel	Partial model	SA/V ratio, temperature, and time challenge
Filter/product compatibility	Filtration	Partial model	SA/V ratio challenge
Chromatography resin lifetime (impact on virus/impurity clearance)	Chromatography	Full model	Cycle number challenge
Reprocessing : Re-filtration	Filtration (micro-filtration or ultra-filtration)	Partial model	SA/V ratio challenge, number of re-filtrations challenge
Impurity spiking experiments	Chromatography, filtration or ultrafiltration	Full model	Worst case Load

Traditional Downstream Process Validation:
Qualification of Small Scale Models

- Qualification of models should focus on the aspects of the model that are most required.
  - Full models:
    - Typically compared to pilot, clinical or manufacturing scale data under target operating conditions
    - Relevant parameters and materials are consistent between scales
    - Quality attribute and performance measures are selected for comparison based on intent of use of the model and may be compared statistically
    - Other measures may be compared qualitatively, (e.g. chromatographic profiles)
  - Partial models:
    - Typically justified theoretically based on scientific and engineering principles
  - Typically discussed in Sections 3.2.S.2.6 or 3.2.A.2 of MAA
    - Description of the model and justifications for its qualification
  - For traditional approach, models are typically qualified one time, in preparation for marketing authorization.
  - Post-approval process changes may require a model to be re-qualified.

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