ICH Q9 Risk Management
Practical Applications for ATMPs – An AAV Case Study

Cynthia Cowgill, Gene Therapy Regulatory CMC,
BioMarin Pharmaceutical Inc.

21 October 2021

Comparability – ICH Q5E

Manufacturers frequently make changes to manufacturing processes during clinical development and post-approval:

e.g. replacing animal derived materials, increasing purity/consistency/yield, site transfers, formulation changes

The goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy.

This is achieved via collection and evaluation of relevant data to determine if the process change has had an adverse impact on the drug product.

Data will include analytical testing, biological assays, and in some cases non-clinical and clinical data.

- i.e. in cases where the relationship between specific quality attributes and safety and efficacy has not been established

Questions and Answers: Comparability Considerations for ATMPs (EMA/CAT/499821/2019)

Q3: How does the risk-based approach (RBA) apply to comparability exercises for ATMPs?

"The potential impact of the proposed change should always be evaluated for its risks to the quality of the final product and the impact on the efficacy and safety profile of the product. The overall extent of the comparability exercise for ATMPs should therefore be driven by a risk-based approach (RBA). Namely, the RBA should be used to determine an appropriate amount of comparability data and to select a suitable set of relevant critical quality attributes (CQAs) to be compared, taking into account the stage of product development and the number of batches available.

Changes that are considered to have a high risk/impact will require an extensive exercise of comparison at the in-process control level, characterization and release. Whenever relevant, the generation of additional/new validation data has to be taken into account. On the other hand, low risk/impact changes may entail a more limited amount of comparability data. A more comprehensive data package is required to support manufacturing changes in pivotal clinical trials or to the marketing authorization."

Quality Risk Management – ICH Q9 Revision and Application

Two primary principles of quality risk management (QRM):

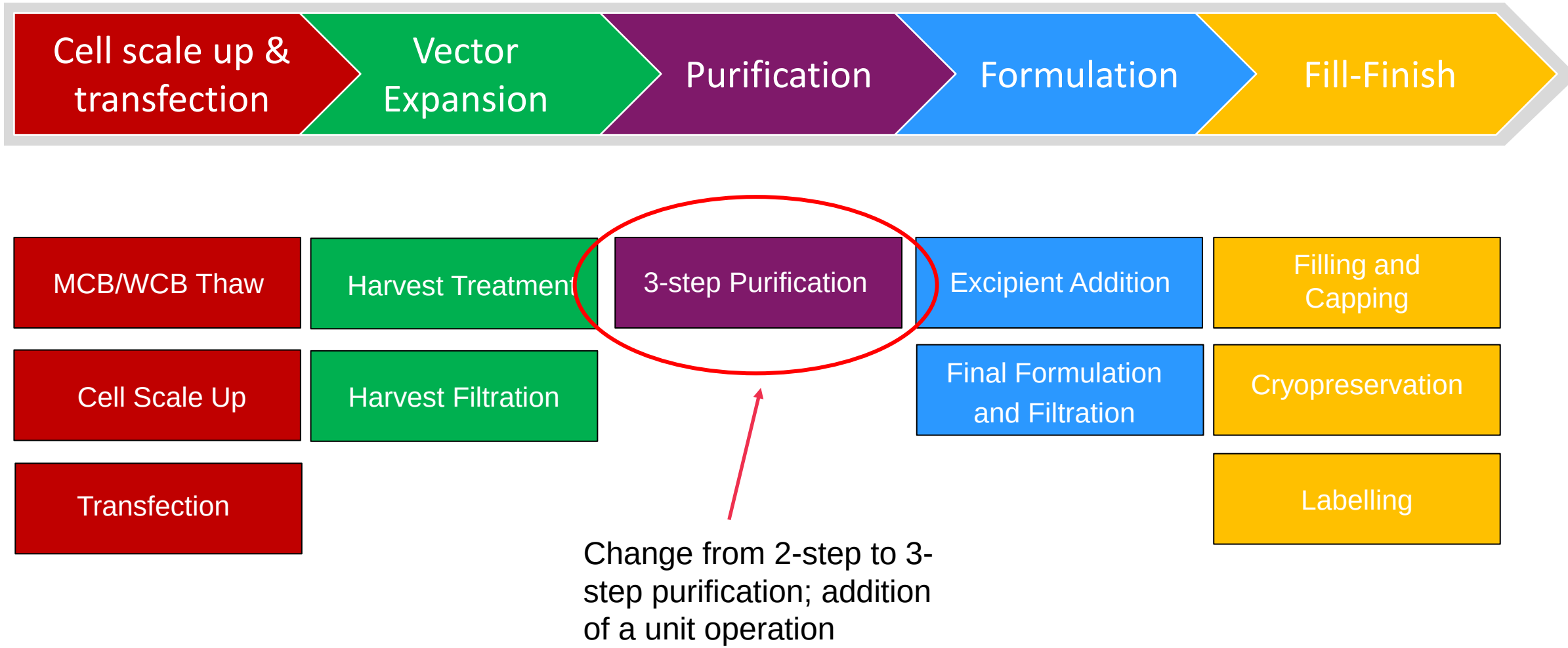
1. The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
2. The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

The ICH Q9 revision in progress is seeking to formalize quality risk assessments (QRA) and make them a **proactive** tool to drive continual improvement.

AAV Case Study – Early Phase AAV Manufacturing Process

MCB/WCB Thaw	Harvest Treatment	2-step Purification	Excipient Addition	Filling and capping
Cell Scale Up	Harvest Filtration		Final Formulation and Filtration	Cryopreservation
Transfection				Labelling

Change in Process to Support Product Manufacturing for Pivotal Study



Rationale for Process Change

Process Component	Ph1/2 Process	Pivotal Process	Rationale for change
Purification	2-step purification process	3-step purification process	Increase process robustness. Further reduce product and process related impurities.

Determine Potential Risk of Process Change – Assessment of Product CQAs

Critical Quality Attribute (CQA) – ICH Q8 (R2)

"A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product."

- CQAs are the foundation for managing product quality throughout all stages of the product lifecycle and defining the control strategy

- Assessment of the impact of the proposed process change on our defined product CQAs, based on current available process and product knowledge, allows us to determine the potential risk/impact of the change

- This will help to determine the CQAs to explore in the comparability study and the amount of data required to assess comparability, e.g. batch numbers to test, testing points in the process, additional characterization required, side-by-side testing, etc.

AAV Critical Quality Attributes

Attribute	CQA	Attribute	CQA
Identity	Vector capsid ID	Potency	BioAssay trans-protein activity
Identity	Vector genome ID	Safety	Viral contaminants
Purity	Capsid titer	Safety	Mycoplasmas
Purity	Residual host cell DNA	Safety	Bioburden
Purity	Residual helper DNA	Safety	Replication Competent (rc) AAV
Purity	Residual host cell protein	Safety	Appearance
Purity	Residual benzonase	Safety	pH
Purity	Aggregation	Safety	Osmolality
Potency	Vector genome titer	Safety	Endotoxin
Potency	Infectivity	Safety	Subvisible particles
Potency	BioAssay trans-protein antigen	Safety	Sterility

List of CQAs modified from J. Wright 'Quality Control Testing, Characterization and Critical Quality Attributes of Adeno-Associated Virus Vectors Used for Human Gene Therapy' Biotechnol J. 2021 Jan;16(1)

CQA Assessment for Proposed Process Change

- ICH Q5E – *"The process assessment should consider such factors as the criticality of the process step and the proposed change, the location of the change and potential for effects on other process steps, and the type and extent of change"*

Scoring Guideline

Risk Score	Guidance
High	Change has potential to significantly impact CQA
Medium	Change has potential to minorly impact CQA
Low	Change has no known or expected impact to CQA

- Use process and product knowledge to date. If gaps in knowledge are observed: Can you do any development work beforehand to gain more knowledge? Are there other similar products you can leverage information from? Literature references?
- Living document, e.g. Repeat the assessment once further knowledge has been gained.

CQA Assessment for Introduction of Additional Purification Step

Attribute	CQA	Impact	Notes
Identity	Vector capsid ID	Low	No expected impact
Identity	Vector genome ID	Low	No expected impact
Purity	Capsid titer	Medium	~15% reduction in empty capsids observed during process development experiments to date
Purity	Residual host cell DNA	Medium	Reduction in residual DNAs observed – will not be detrimental to product quality / patient safety.
Purity	Residual helper DNA	Medium	
Purity	Residual host cell protein	Low	No expected impact
Purity	Residual benzonase	Low	No expected impact
Purity	Aggregation	Medium	Minor reduction
Potency	Vector genome titer	Low	No expected impact
Potency	Infectivity	Low	Minimal reduction in vector aggregates expected
Potency	BioAssay trans-protein antigen	Medium	Potential impact to potency due to decrease in empty capsids, product dose (based on vg titer) will not be impacted therefore no impact on safety or efficacy
Potency	BioAssay trans-protein activity	Medium	

* Assumed no impact on safety methods for this process change

Outcome

- Low impact of process change determined after scoring using prospective quality risk assessment tool – can feed this into the comparability study design:
  - Take into account the stage of development
  - Prior process development work allows good understanding of the potential impact of the change based on data
  - Allows us to concentrate on those CQAs which are most impacted, with limited characterisation assays required
  - Proposal of 1-2 batches using new process with defined acceptance criteria from historic batch data for assessment of comparability

Conclusions

- A risk based approach should be used to determine the appropriate amount of data to generate as part of assessment of comparability with suitable, relevant CQAs to be compared

- The principles of ICH Q9 can be used to formalize assessment of the risk/impact of the proposed process change(s) based on current knowledge and the results can feed into the design of the comparability study

- Allows identification of relevant CQAs to study and with a phase appropriate approach can help to indicate a suitable amount of data to generate