# Leveraging platform and process characterization data to accelerate CGT validation and commercialization

**Authors: Sanjay Nilapwar (AbbVie), Marcos Sousa, Bernd Tscheschke (Bayer), Kayla Garrett , Christopher Boyd (Pharmaron), Silvia Gomez (Bayer (Viralgen)), César Trigueros (Bayer (Viralgen)), Ane Quesada (Bayer (Viralgen)), Vineet Kumar, Kevin Stanson (Roche) ,Yuanli Song (Sanofi), Brian Mullan (Yposkesi), Kathleen O'Hagan (BioPhorum)**

**Contributors: Lingling Xia (AbbVie), Stefan Sievers (Bayer), Brittany Mertens (Biogen), Laura Fagan, Kieron McIntyre (Pharmaron) Ian Sebastian, Gwyn Tessitore, Tom Tully (PTC Therapeutics), Jordan Byrd (Regeneron), Michael Winkler (Regenxbio) Sudha Babu, Sven Markert, Jakob Wisbauer (Roche), Séverine Buffet (Yposkesi)**

## Summary

Streamlining process development and validation activities for cell and gene therapy (CGT) products is highly beneficial to ensure timely availability of therapies to patients and to maintain sustainable product pipelines. There are several mechanisms that can contribute to an overall reduction in program timelines, primarily involving leveraging process development data and/or the use of process platforms to support manufacturing and validation. This poster summarizes the work by done by 16 member companies for BioPhorum ATMP Phorum that have produced a deliverable that defines requirements and options for leveraging across projects for CGT development. This paper aims to provide points to consider regarding how companies can utilize prior knowledge and platforms to leverage process characterization to reduce testing and/or studies required during process validation for drug substance (DS) and drug product (DP) manufacturing processes. Any approaches used to expedite validation and commercialization should be employed with due consideration of regulatory requirements and guidelines. Many of the recommendations discussed in this poster are primarily applicable to gene therapies (GTs.) Due to the increased complexity associated with cell therapies (CTs), practical recommendations are limited. However, the concepts outlined may still be applied to develop an individual company's manufacturing platform and/or leveraging strategy. Additionally, these concepts may be applied to batch or continuous manufacturing processes as applicable.

## Regulatory considerations

For developing and characterizing pharmaceutical production processes, and detailing the production process and its controls in regulatory dossiers, there is a well-established regulatory expectation that a commercial pharmaceutical manufacturing process is:

- Defined (unit operations, their order/sequence and functionality)
- Characterized (the linkage between process parameters and product quality is understood)
- Validated (the manufacturing process is evaluated and deemed to be robust, and reliably gives the intended outcomes).

There is an expectation that the level of development, understanding and control progressively increases in a phase-appropriate manner (requirements for investigational new drug (IND)/investigational medicinal product dossier (IMPD) submission > process validation > commercial submission). Approaches to phase-appropriate development are reasonably well established for other product categories such as monoclonal antibodies (MAbs), but are less well defined for CGT. For CGT products, the number of batches and experience gained at each stage is likely to be substantially less than that gained for other product modalities.

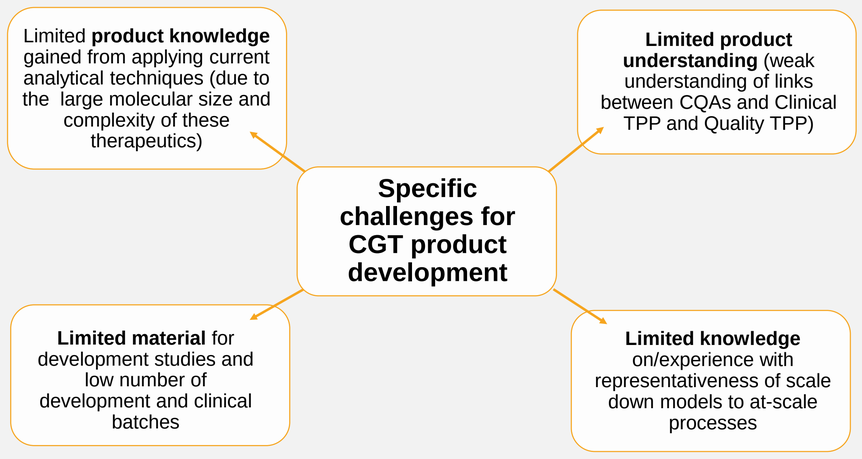
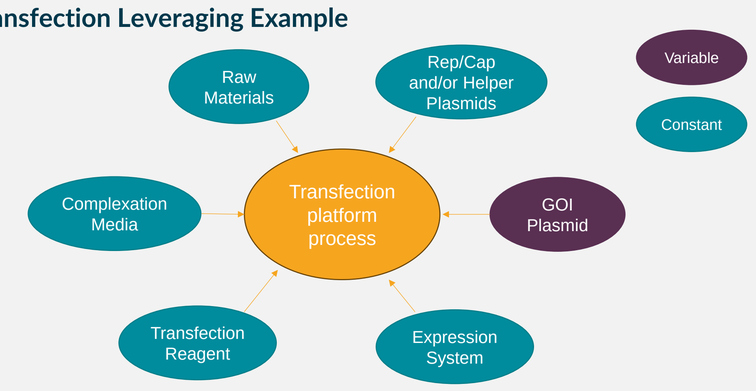



*Figure 1: Scheme of specific challenges for CGT product development*

In a general sense, applicable to most therapeutic products regardless of their modality, fundamental expectations for process characterization and validation are defined in guidance documents from the International Conference on Harmonisation (ICH), the European Medicines Association (EMA), and the US Food and Drug Administration (FDA), among other sources. In essence these requirements should form the basis for a regulatory platform for a systemic approach to the development of CGTs, following the guidelines **ICH Q8; ICHQ9, ICHQ11 and ICHQ10.**

## Transfection leveraging example

### Transfection Leveraging Example




### Potential process parameters that may exhibit GOI-specific sensitivities

**Complexation**
- Concentration of transfection reagent
- Complexation time
- Transfection reagent ratio
- Quality of plasmid
- Plasmid ratio

**Transfection**
- Cell density at transfection
- Final DNA complex concentration
- Cell culture conditions at transfection
- Duration of transfection

**Post-Transfection**
- Transfection to harvest duration
- Post-transfection cell growth conditions

## Gene Therapies: Platform Examples

Platform processes may be established considering two components:

**a common production system** and/or a **related group of products**.

**Production System:** consider Devices and Technology, Starting Materials, Processing Conditions, or Process/Product Specifications.

Production systems aligned from development through manufacturing can be maintained with reasonable expectation of consistent product quality.

**Related group of products:** the production process of each product are similar enough such that an essential proportion of the production system is aligned.

The related group of products may share common physical and chemical properties.

*Figure 2:Consensus platform definition based on a survey of 20 companies.*

Examples of platform approaches may include:

- **For gene therapy, the changing of one transgene in a given AAV serotype for another**
- **For cell therapy, the changing of cell collection source or gene editing raw materials**

## Opportunities to Leverage Across Industry

Approaches coming from other product categories such as biologics

Specific to gene therapies

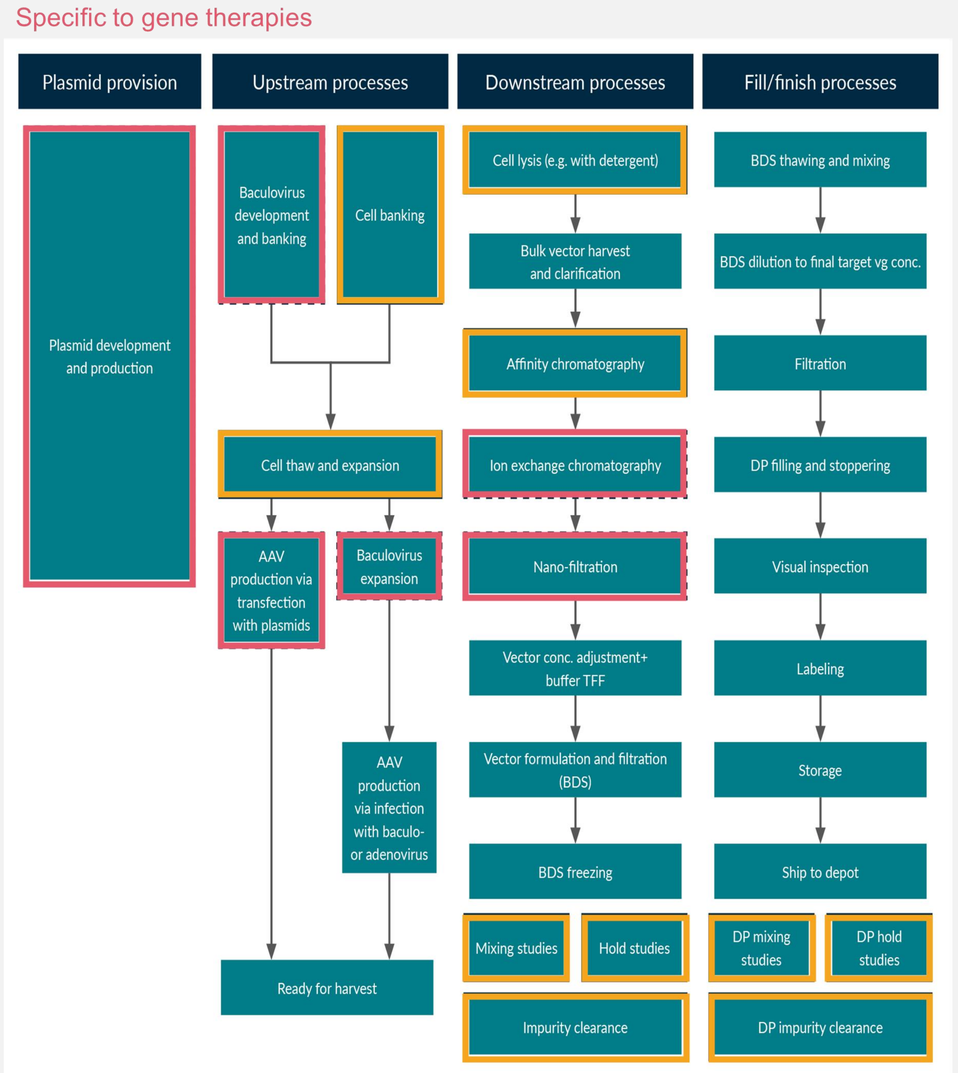
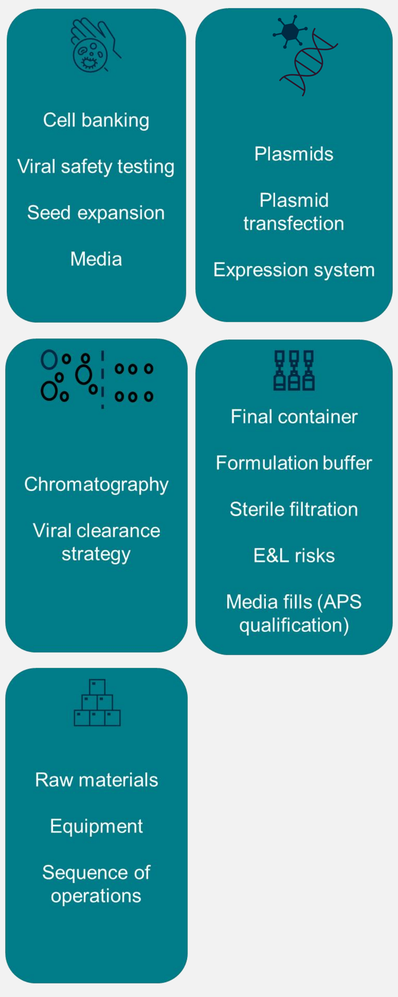



*Figure 3: An overview of DS and DP manufacturing unit operation for a gene therapy viral vector.*

- Areas where leveraging or platform approaches may be applied:



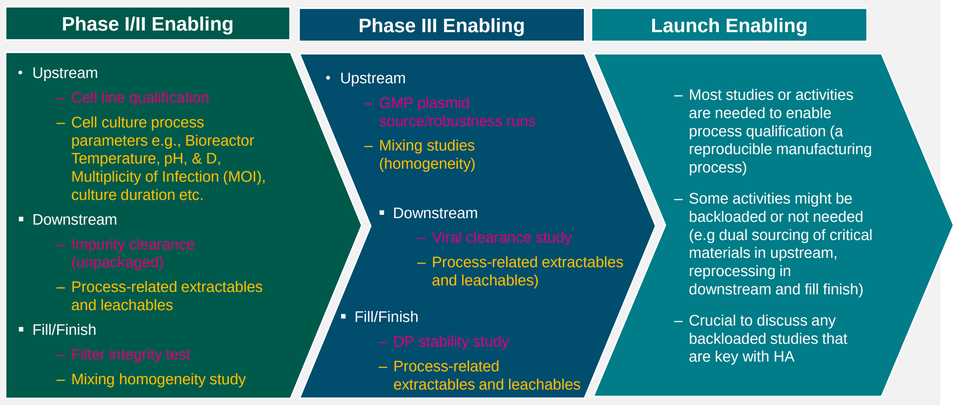

## Phase appropriate process development and characterization

### Phase appropriate process development and characterisation – Sample Unit operations/Activities in DS/P GT Production

- Recommend designing the manufacturing process as early as possible
  - Allows knowledge building and use of historical data to reduce risk and mitigate comparability challenges
  - Need to weigh the cost and benefit of process optimization at each stage of development
- Some studies are performed based on regulatory recommendations/needs
- Phase appropriate process development and characterization can be key in accelerating process validation and commercialization of GT

### Phase appropriate process development and characterisation –Study timing based on regulatory and business considerations

- Sponsors are expected to produce safe and efficacious product for patients
- Regulatory agency understands information about a molecule and process can be limited in early stages; this is expected to change as molecule development progresses
- Some studies/activities may be carried out early or later in development depending on regulatory guidelines or business risks/opportunities the sponsor can take




- Recommended based on existing regulatory guidelines or technical knowledge considerations
- Recommended based on studies that can be strategically added to mitigate business risk

## Conclusions

Platforms for development of manufacturing processes and analytical methods are well established for numerous therapeutic modalities. These enable significant efficiency gains in development programs by leveraging systems and approaches that were developed for earlier products, often by establishing platforms, and aggregating and analyzing data across different development programs within the same modality to continuously increase understanding and insights. For well-established product classes such as MAbs, platforms can significantly reduce the cost and time to bring new therapies to market.

For CGTs, sufficient experience does not exist today to enable this, so in this white paper member companies from BioPhorum have provided strategies and best practices to enable CGT developers to create platforms for the development of their products.

The white paper produced outlines various aspects of product development that are key to bringing CGT to market, such as process development and different technical evaluations for E&L, viral safety and mixing studies. For each section a high-level 'how to' guide is provided, followed by suggested strategies for leveraging internal company or cross-industry approaches. An overview of regulatory requirements is provided at the beginning of the document, and a section on control strategies provided at the end, to tie the various elements together. Applicable approaches from other product classes are highlighted, as well as CGT-specific approaches.

## References

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2. ICH Q8 (R2), Pharmaceutical development, Step 4, August 2009.
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