AAV Process Development Guidance Based on Cost Modeling

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Introduction

Production of adeno-associated virus (AAV) and other viral vectors used for gene therapy faces challenges due to high manufacturing costs and process development timelines which may be considerably shorter than what has been used for more traditional biopharmaceuticals. Many process development activities may be undertaken to reduce manufacturing costs, but these costs are often not directly related to the process improvements being considered. In this work, process and cost models were built for AAV production and analyzed to assess the holistic impact of common process development objectives on the manufacturing costs. The insights from these analyses provide guidance for prioritization of various process development objectives.

Evaluating process development activities

Costs

- Type, amount, and/or cost of available resources
- Pipeline and other opportunities
- Time required

Impact

- Likelihood and magnitude of success
- Fit with existing facilities, platforms, etc.
- Reduction of cost of goods manufactured

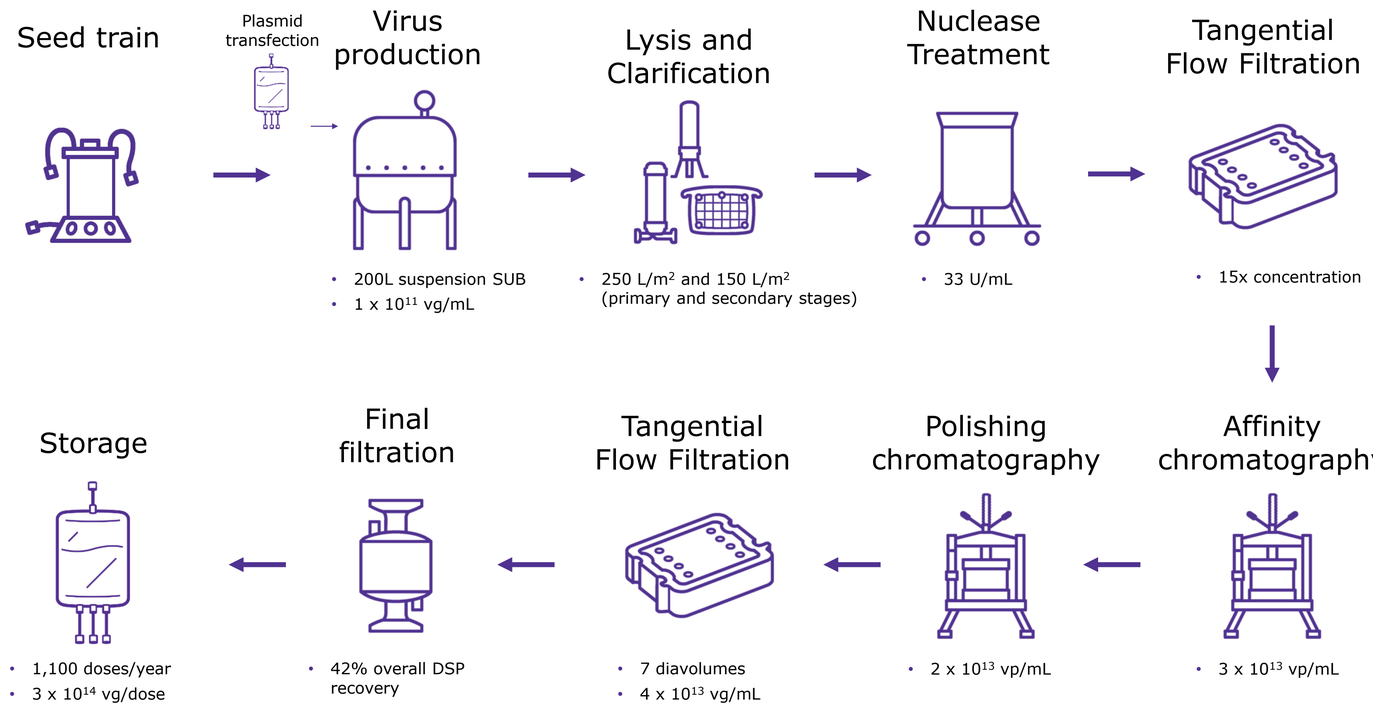
Methods

- Process parameters were determined from survey of AAV manufacturing experts both internal and external to MilliporeSigma
- Process and cost models were built using BioSolve™ software (version 7.6.1.1) in collaboration with BioPharm Services assuming:
  - New, single-product facility (green field)
  - Bulk drug substance production
  - Single-use manufacturing process
- Pricing for raw materials, equipment, and consumables from internal MilliporeSigma sources
- Economic assumptions such as depreciation rates, insurance costs, and labor rates from standard BioSolve™ default values

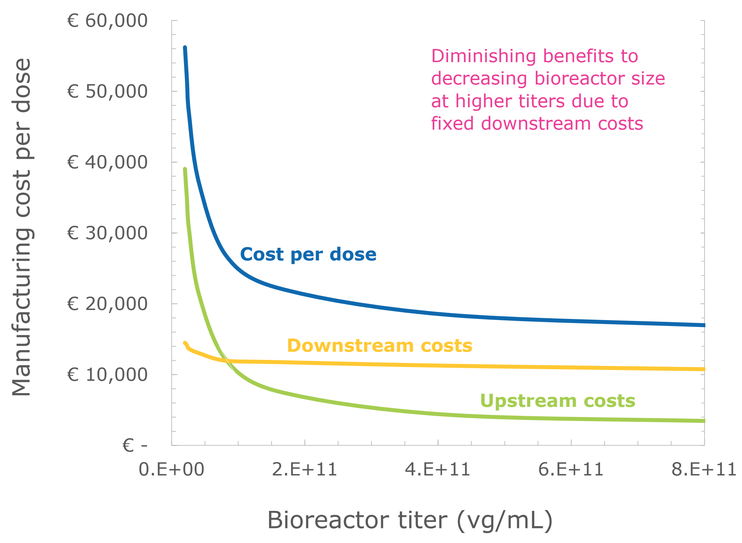
Conclusions

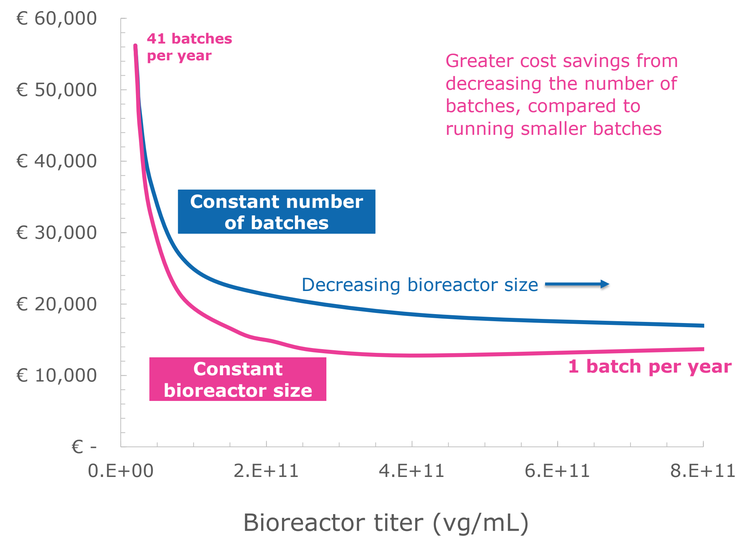
Cost modeling can be a powerful tool to assist with prioritizing areas of focus for process improvement during process development. It is especially useful for processes producing viral vectors for gene therapies (e.g. AAV) due to the limited practical commercial experience and the short timelines during development. The results from this work emphasize the importance of understanding the relative costs of each part of a given process. For example, while making upstream improvements such as increasing the titer may reduce upstream costs, downstream costs may be largely unchanged, limiting the potential impact of further titer improvements. Likewise, improvements to reduce the usage of consumables such as chromatography resins have little impact on other fixed costs such as capital. An early understanding of these costs relationships can aid in developing a rational strategy to process development.

AAV Manufacturing Process

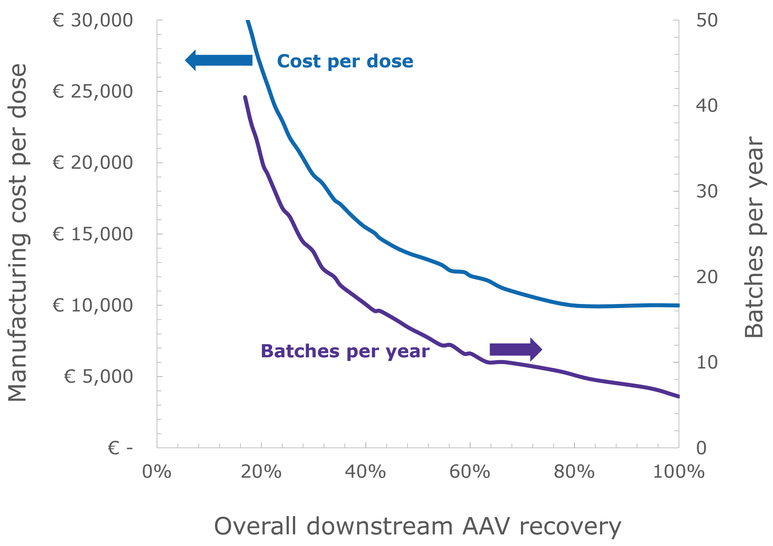


Increasing AAV titer at harvest

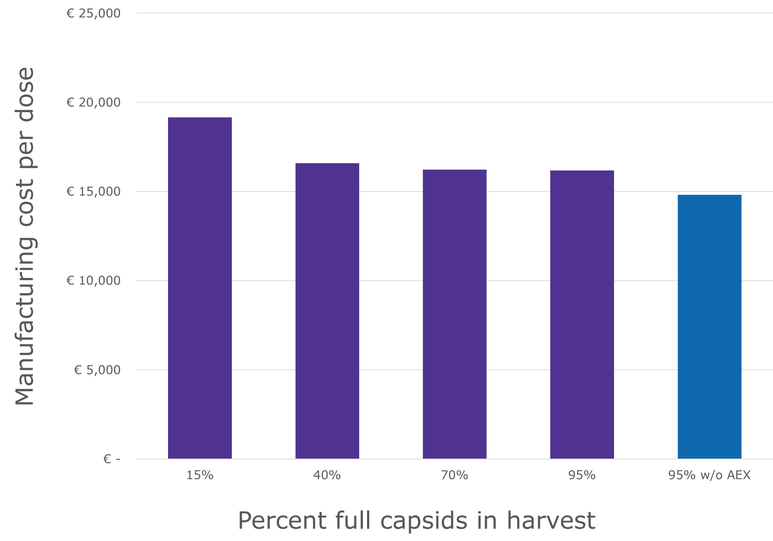




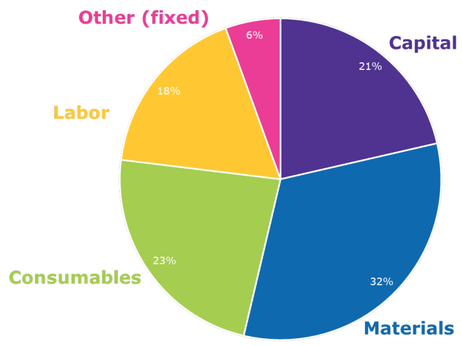
Increase recovery throughout DSP



Decrease empty AAV capsid production in bioreactor



Relative costs



Increasing downstream recovery to reduce number of batches can help reduce costs such as materials, labor, and consumables. Fixed costs are not reduced.

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