A Comparative Cost of Goods Analysis of dbDNA™ and Plasmid DNA For AAV Gene Therapy Manufacturing

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TOUCHLIGHT

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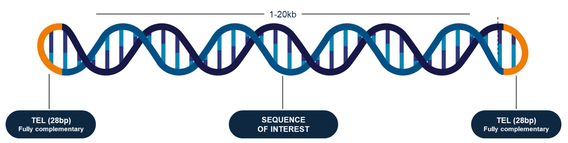
INTRODUCTION

Recombinant adeno-associated virus (AAV) remains a critical tool for gene therapy. However, high dose requirements of up to 1e+17 VG/dose[1] and complexities of AAV production make these therapies exceptionally costly, with therapy prices reaching $3.5 million[2]. A major hurdle to overcome in efforts to reduce AAV cost of goods (COG) is the current reliance on GMP-grade plasmid DNA (pDNA), which contribute up to 40% of the total AAV batch cost[3].

Doggybone DNA (dbDNA™) represents a cell-free alternative to pDNA for AAV production which is manufactured to GMP using a rapid, high fidelity amplification process that has been adopted by numerous developers with kilogram-scale commercial demand. It has been shown that dbDNA yields comparable viral genome titres and up to 2-fold greater % full AAV capsids in comparison to pDNA, whilst requiring 40% less total DNA for transfection[4].



Advantages of dbDNA for AAV manufacturing:

- ✓ **Cost of Goods -** Less DNA & transfection reagent for improved viral genome titres
- ✓ **Purity -** Increase full capsid percentage & full-length AAV genomes
- ✓ **Safety -** Reduce bacterial impurities & mispackaging of contaminant sequences

In this study, an independent analysis was performed by **Decisional Points Limited** to quantify the reduction in COG achievable for AAV gene therapy developers who have switched to dbDNA for AAV manufacturing.

METHODS

Using **Decisional Point's** established AAV bioprocess economic model, a baseline COG analysis was performed to compare dbDNA to pDNA for AAV manufacturing. The key contributing factors to overall COG at various dose sizes were also identified.

Subsequently, a scenario analysis was performed to determine the impact of adjusting a number of key parameters on COG. These included dose size, GMP DNA cost, and amounts of DNA and transfection reagent for transfection. This analysis allowed for simulation of various scenarios which could be realised when switching from pDNA to dbDNA, including further transfection process optimisation with dbDNA. The assumptions used for each analysis are presented in Table 1.

Parameter	Baseline Analysis Value	Scenario Analysis Value
Dose Size (Viral Genomes/Dose)	5e+15	1e+15 – 2.5e+16
Doses/year	2,500	
% Decrease in DNA unit cost with dbDNA	27	0 – 50
Transfection reagent unit cost (k$/L)	50	
Total DNA concentration (µg/1e+6 cells)	**dbDNA-** 0.6 **pDNA-** 1.0	**dbDNA-** 0.5 - 0.6 **pDNA-** 1.0
Transfection Reagent : Total DNA Ratio (L:g)	3 : 1	**dbDNA-** 1 – 3 : 1 **pDNA-** 3 : 1
Viral Genome Titre at Harvest (VG/L)	1e+14	
Total Viral Genome DSP Recovery (%)	40	

Table 1: Baseline & Scenario COG Analyses Assumptions

RESULTS

A breakdown of the key contributors to COG at selected dose sizes is presented in Figure 1. The cost of DNA and transfection reagent were found to be key contributors to COG, with the cost of DNA contributing approximately two-fold more to COG than the cost of transfection reagent. The contribution of DNA and transfection reagent to COG reached up to 26% and 13% respectively at the highest dose size evaluated.

The baseline analysis revealed that switching from pDNA to dbDNA, without transfection process optimisation, reduced COG per dose by 14%, which represents a saving of approximately $15M per year or $6k per dose (Figure 2 & Table 2). Furthermore, transitioning to dbDNA was found to reduce the cost of the production bioreactor step by 23%.

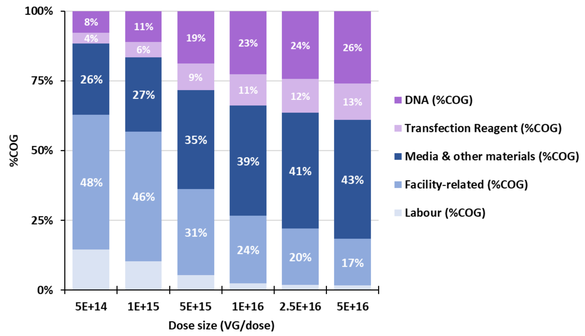


Figure 1: Key COG contributors at each dose size

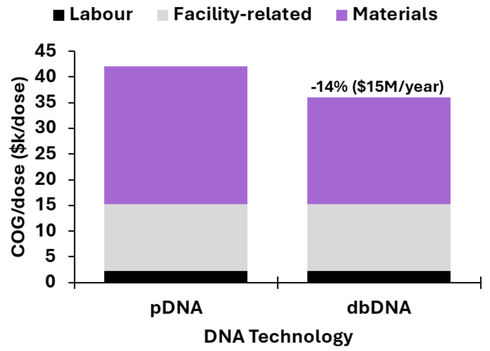


Figure 2: Baseline COG analysis evaluating the effect of switching from pDNA to dbDNA upon cost of goods per dose

In the scenario analysis, selected scenarios and their effect on COG relative to pDNA were modelled and are presented in Figure 3 & 4.

At the highest dose size evaluated, overall COG and production bioreactor step COG savings of 18% and 26%, respectively were predicted when switching to dbDNA.

Iterative COG savings achieved through optimisation of dbDNA transfection conditions are also shown, culminating in overall COG savings of 20% (Figure 3) and a COG per dose saving of $8k/dose or $21M per year.

When optimised dbDNA transfection conditions are combined with a 50% lower DNA unit cost for dbDNA compared to pDNA, COG/dose savings with dbDNA increase to $9k/dose, equating to 22% or $23M per year (Figures 3, Figure 4 & Table 2).

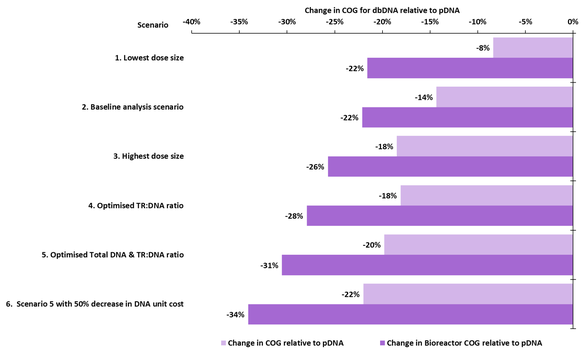


Figure 3: COG scenario analysis results. Effect of dose size, dbDNA transfection parameters, and DNA unit cost on COG

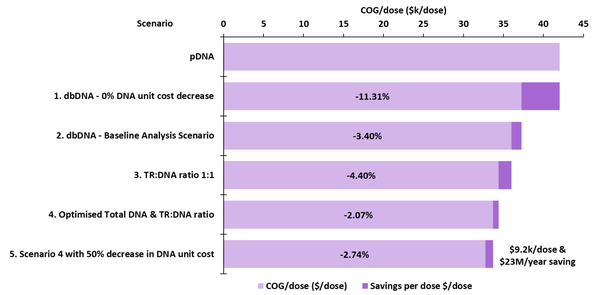


Figure 4: COG scenario analysis results. Effect of dbDNA transfection parameter optimisation and DNA unit cost on COG per dose.

Cumulative cashflow savings across the lifecycle of an AAV gene therapy product were calculated and could exceed $60M, with the present value of those cashflows exceeding $20M.

CONCLUSION

AAV gene therapy developers can realise significant economic advantages by choosing dbDNA, accelerating the drive towards more cost-effective AAV gene therapies. Further COG savings beyond those modelled in this study could be achieved when switching to dbDNA due to the elimination of the need for bacterial MCB manufacture and efficiencies in downstream processing with improvements in % full capsids.

Scenario	COG	% COG Saving	Potential $ Saving/year
Baseline	**Production Bioreactor Step**	**23%**	**$15M**
	Overall	**14%**	
Optimised dbDNA Transfection Conditions	**Production Bioreactor Step**	**34%**	**$23M**
	Overall	**22%**	

Table 2: Summary of dbDNA COG analysis results

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