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USE OF A PARALLEL BIOREACTOR SCALEDOWN SYSTEM FOR OPTIMISATION OF A PERFUSION-BASED UPSTREAM PROCESS FOR ADENOVIRUS PRODUCTION

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The recent pandemic emphasises the need for vaccine producers to be able to respond rapidly to the need for large quantities for global distribution. Here, we report work to optimise a perfusion-based upstream approach. Perfusion can enhance volumetric productivity of adenoviral vectors, but the complexity of perfusion culture and the lack of suitable scale-down models has hindered work to establish the complex relationships between variables affecting the process.

Here, we described what we believe to be the first publicly-disclosed use of a scale-down parallel perfusion bioreactor system (Ambr250 Perfusion, Sartorius). Using this system, we were able to apply a design of experiment (DoE) approach to explore the effect of three variables upon virus productivity: perfusion start time; high or low viable cell density at infection; and duration of intensified perfusion. The results indicated that longer intensified perfusion duration significantly improved both cell-specific productivity and volumetric productivity. Furthermore, we observed that using the lower range of viable cell density at infection significantly improved cell-specific productivity. We also found that the effect of perfusion start viable cell density was not statistically significant, but trended towards increased productivity with earlier perfusion start.

Process development must balance multiple considerations (for example productivity versus medium consumption). Use of the Ambr250 perfusion scale down model has supported our development of a manufacturing process designed to maximize output of ChAdOx1-based adenovirus-vectored vaccines, while retaining simplicity and suitability for existing manufacturing facilities.

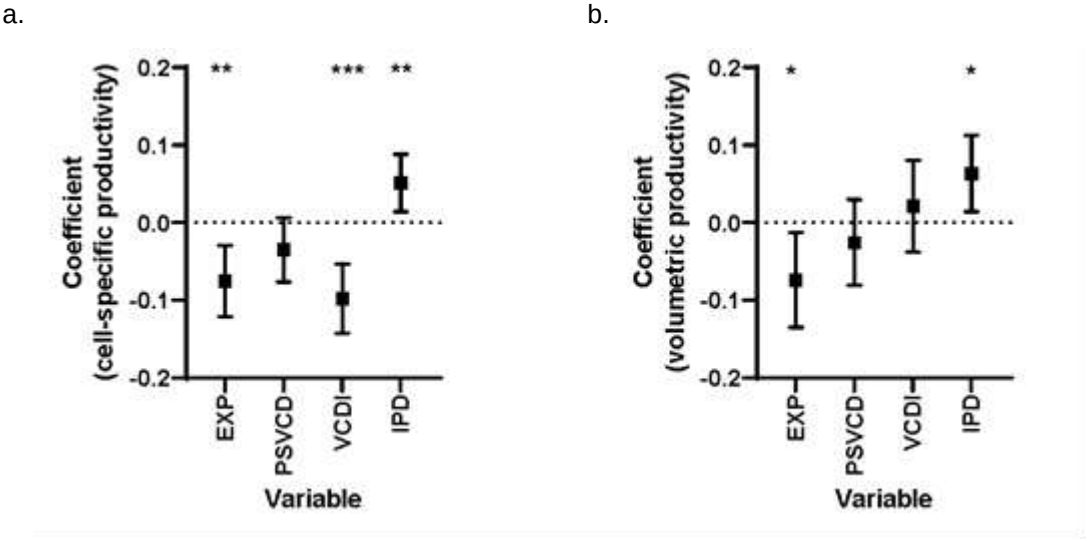

*Fig 1 (**a–b**) - Modelled coefficients for the four factors for each of the two productivity response variables; error bars show 95% confidence intervals. *p < 0.05, ** p < 0.01, *** p < 0.001 (t test).*
Abbreviations: EXP, experiment; IPD, intensified perfusion duration; PST, perfusion start time; PSVCD, perfusion start viable cell density; VCDI, viable cell density at infection.