A risk-based model was built to evaluate the benefits of fermentation perfusion and how this would integrate with an existing plant.

Risk-based approach used backup perfusion vessels to minimize the effect of disruption to downstream purification processing.

Excess capacity from the production train was used to create a small-scale ‘plant-within-a-plant’ for clinical and small-scale production.

The completed design showed a positive NPV of $40MM over 5 years.

Perfusion technologies have shown potential to radically improve cell densities in fermentation over batch-based technologies, with titers an order of magnitude higher than those achieved in existing facilities. Such high titers enable much smaller fermentation vessels to be used, minimizing plant clean-space requirements and maximizing often limited downstream purification train resources.

One of the big issues with fermentation perfusion remains the radically different operating characteristics of perfusion technologies. Since the transient time for perfusion is months longer than a batch-based system, contamination risk increases considerably. Bioproduction Group’s brief was to create a feasible perfusion platform that would fit into an existing plant. The goal was to enable the manufacturer to use both perfusion technologies for new products as well as the traditional batch-based process for legacy products.

Realizing that contamination risk would be critical to the evaluation of this technology, Bioproduction Group collected historical contamination data based on transient time in existing batch-based systems to estimate the ‘per-day probability of failure’. Monte Carlo techniques were then used in conjunction with Bio-G’s facility simulator to estimate when a perfusion vessel would become contaminated, and what the effect would be on production.
“Making perfusion work is all about mitigating the effect of contamination”, comments Principal Rick Johnston. “Making sure that backup perfusion vessels, inoculum at the correct scale, and even media is available at all times is critical to success.” After extensive consultation with the manufacturer, redundant capacity was added to the perfusion train to allow operations to continue even if a vessel was contaminated.

Bioproduction Group then produced a comprehensive simulation model of fermentation perfusion technologies to show how they could be used in ‘semi-batch’ mode with existing (batch-based) purification equipment. Unused scale-up tanks were re-tasked to produce clinical and small-scale production, allowing the plant to produce multiple products at very different scales at the same time.

Bio-G’s recommendations were to segregate production into a small-scale batch-based production train and a large-scale perfusion fermentation train, retaining the ability to operate the plant in large-scale batch mode. The resulting design increased the plant’s capacity to simultaneously operate as a launch platform for new products, as well as perform technology transfer and optimally utilize workers in the plant.

More importantly, the output of the simulations showed that this change would allow the company to produce significantly more material without large-scale engineering changes. The NPV of this scenario was $125MM over 4 years.