A COMPLETELY AUTOMATED HIGH INOCULATION DENSITY FED BATCH PROCESS THAT ACCOMMODATES CLONAL DIVERSITY AND ROUTINELY DOUBLES SPACE TIME YIELD AS COMPARED TO LOW INOCULATION DENSITY PROCESSES

Brandon Downey, Lonza Biologics R&D
brandon.downey@lonza.com
Mikayla Olin, Lonza Biologics R&D
Nicolas Wolnick, Lonza Biologics R&D
Brian Russell, Lonza Biologics R&D
Hunter Crittenden, Lonza Biologics R&D
Julia Armstrong, Lonza Biologics R&D
Shannon Hendrick, Lonza Biologics R&D
Thaddeus Webster, Lonza Biologics R&D
Brian Hadley, Lonza Biologics R&D
Carrie Mason, Lonza Biologics R&D
James Graham, Lonza Biologics R&D

Key Words: Perfused N-1, Capacitance, Raman, Intensification, Automated Feeding

The productivity of the production bioreactor is a dominant cost driver for the manufacture of biopharmaceuticals. Therefore, an effective means to decrease cost of goods for biopharmaceutical manufacture is to increase the productivity of the bioreactor process. We developed an intensified fed-batch process which utilizes a perfusion reactor in the inoculum stage to enable high inoculation density in the production bioreactor. Using this process, we demonstrated space time yield (defined as mass of product produced per bioreactor volume per time) is increased on average 130%, or more than double, compared to space time yield achieved in a legacy low inoculation density platform fed-batch process.
We further demonstrate that this intensified fed-batch process can accommodate cell lines with diverse cell growth and metabolism characteristics, without the requirement to tailor the process recipe for each cell line (Figure 1). The process accomplishes this by incorporating completely automated nutrient feeding in the production and N-1 bioreactor steps, which automatically tailors feed rates to culture demand. Feed automation was accomplished by controlling perfusion feed rate based on capacitance measurement in the perfusion inoculum reactor, and by controlling nutrient feed rates based on nutrient concentrations as measured by Raman spectroscopy in the fed-batch production bioreactor. This automated feeding methodology was shown to mitigate the effects of differences in cell line growth and metabolism, which can be exacerbated in intensified cell cultures because mismatches between culture nutrient requirements and feed supplementation rates can more easily result in limitation or over-abundance of nutrients at the higher cell densities achieved in intensified cultures. The result is a platform process which automatically adapts to variations in nutrient demand and growth rate and robustly produces a substantial increase in space-time yield compared to legacy fed-batch processes.

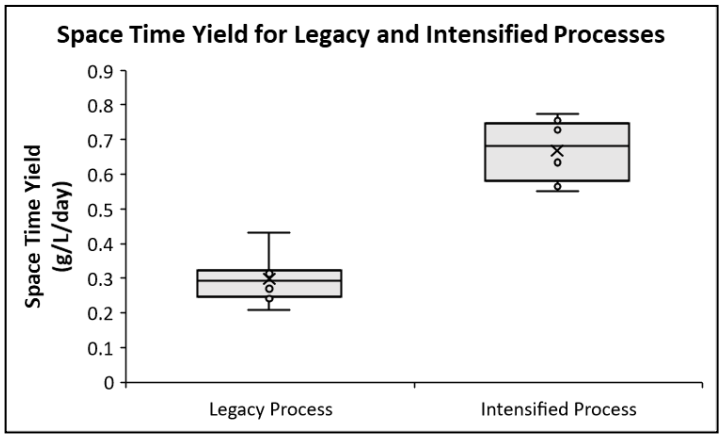

Figure 1 – Space time yield for legacy and intensified fed-batch processes for six clones expressing three different molecules