# Improving Manufacturing Network Productivity: Overcoming the Downstream Bottlenecks

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With a maturing product pipeline and higher dose (and thereby production) requirements for many protein therapeutics, internal manufacturing capacity will be exceeded in the coming years, requiring additional manufacturing facilities and/or outsourcing production to CMOs. Improved manufacturing processes are being developed using a combination of technologies established in other industries, such as continuous processing, and newer concepts to improve manufacturing network productivity and enable process fit into existing plants. In addition, advancements in cell line and culture technologies have led to higher titers (>5 g/L) for monoclonal antibodies coupled with shorter bioreactor duration. This has necessitated the development of higher throughput downstream processes to prevent purification from being the throughput bottleneck in the manufacturing process. The primary bottlenecks reside in the initial purification (capture) step using protein A affinity chromatography with relatively low antibody binding capacity, and in the intermediate product pools and buffer volumes exceeding the capacity of existing production vessels throughout the manufacturing process. Several technologies were evaluated to address these bottlenecks and help improve productivity including (i) newer generation protein A resins with higher binding capacity (ii) semi-continuous and continous modes of chromatography for antibody capture on protein A and (iii) single pass tangential flow filtration coupled to purification steps to enable in-line concentration of intermediate product streams. This presentation will show how integration of these process improvements into the purification process can facilitate debottlenecking and improve