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A Frost & Sullivan White Paper

3M™ Harvest RC
The Need to Re-imagine Clarification

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Rising demand for new monoclonal antibody therapies, stringent requirements to achieve consistent quality, and most importantly, focus on higher productivity is driving biopharmaceutical companies to optimize their downstream processing operations. The typical mAb manufacturing process has several steps, including multiple clarification stages which are the first steps of the purification process.. The clarification train, if not properly designed, negatively impacts yield, purity, and cost.

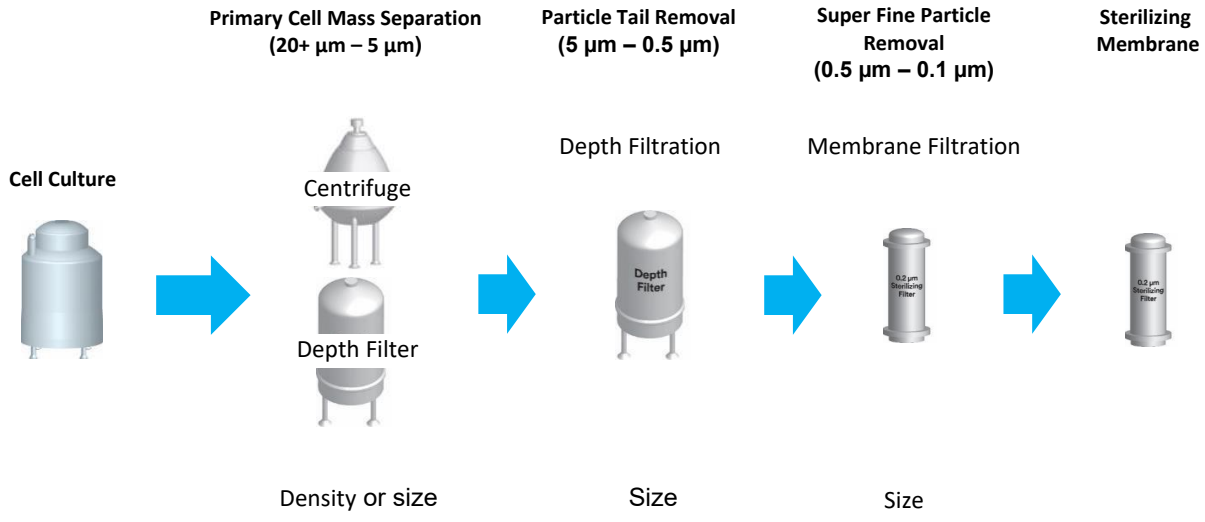
3M™ Harvest RC: The Need to Re-imagine Clarification

Briefly, the primary goals for harvest and clarification operations are to remove cells and cell debris from mammalian cell culture, and further clarify the resulting product in order to capture the mAbs via chromatography downstream.

In cell cultures, it is essentially slurry of contaminants varying in different sizes and shapes. They can range from the host cells to cell debris to much smaller particulates such as DNA, viruses and proteins. As the stream becomes cleaner and purer, the level of separation gets harder as operators/scientists start dealing with soluble contaminants and particle sizes that cannot be removed by simple filtration.

Traditionally, various technologies are used for clarification processes such as centrifugation, tangential flow filtration (TFF), depth filtration, and microfiltration. These methods exploit the differences in “size” to remove large particles such as cells and cell debris.

Figure 1: Legacy Clarification Strategy



Source: 3M

However, the need to achieve higher concentration, compress operations timelines, and increase mAb purity and safety has prompted operators/scientists to carefully evaluate the limitations of these technologies.

The fact that centrifugation may damage sensitive mammalian cells and release undesirable intracellular proteins and DNA is a common challenge. Although operators/scientists have found that TFF and depth filters can reduce this risk, they struggle with large set up times and are beset with large flush volumes to eliminate extractables. Operators/scientists also worry about of the versatility of these technologies to single use bioreactors.

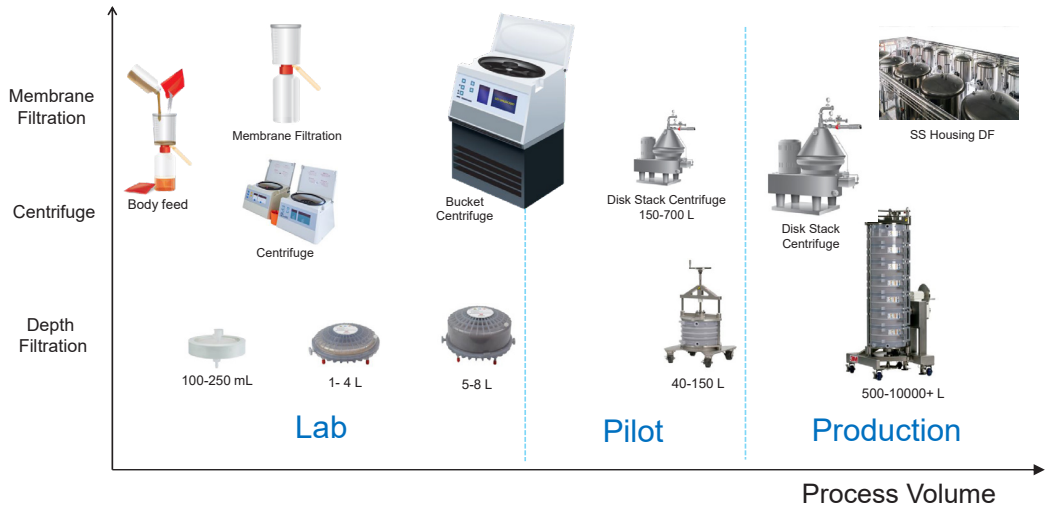
Finally, a major drawback with the current clarification strategies is that there is no single approach that can span all the way from discovery to manufacturing scale. As a result, it is imperative that operators/scientists to examine porous chromatography platforms to get further separation during the capture and polishing steps to truly achieve the resolution and purification levels needed.

Current bioreactor processes producing mAbs with higher drug titers and yields increase cell debris and raise concentrations of organic constituents. The colloidal characteristics of such components severely impede the separation process.

There are different scales of clarification technologies: depth filters, centrifuges, and membrane filters that exist for clarification. The onus is on operators/scientists to work with a combination of these different technologies in order to arrive at the downstream purification steps (Figure 2). The choice of these technologies must also take the requirements for integration with downstream processes, such as ultrafiltration, into account.

As the scrutiny on purification levels rises, operators/scientists will have to be more careful and vigilant in managing variable and unpredictable filtration outcomes from discovery to manufacturing stages. Therefore, operators/scientists will have to consider other approaches that span the entire process scale space.

Figure 2: Current Clarification strategy from Discovery to Manufacturing



Source: 3M

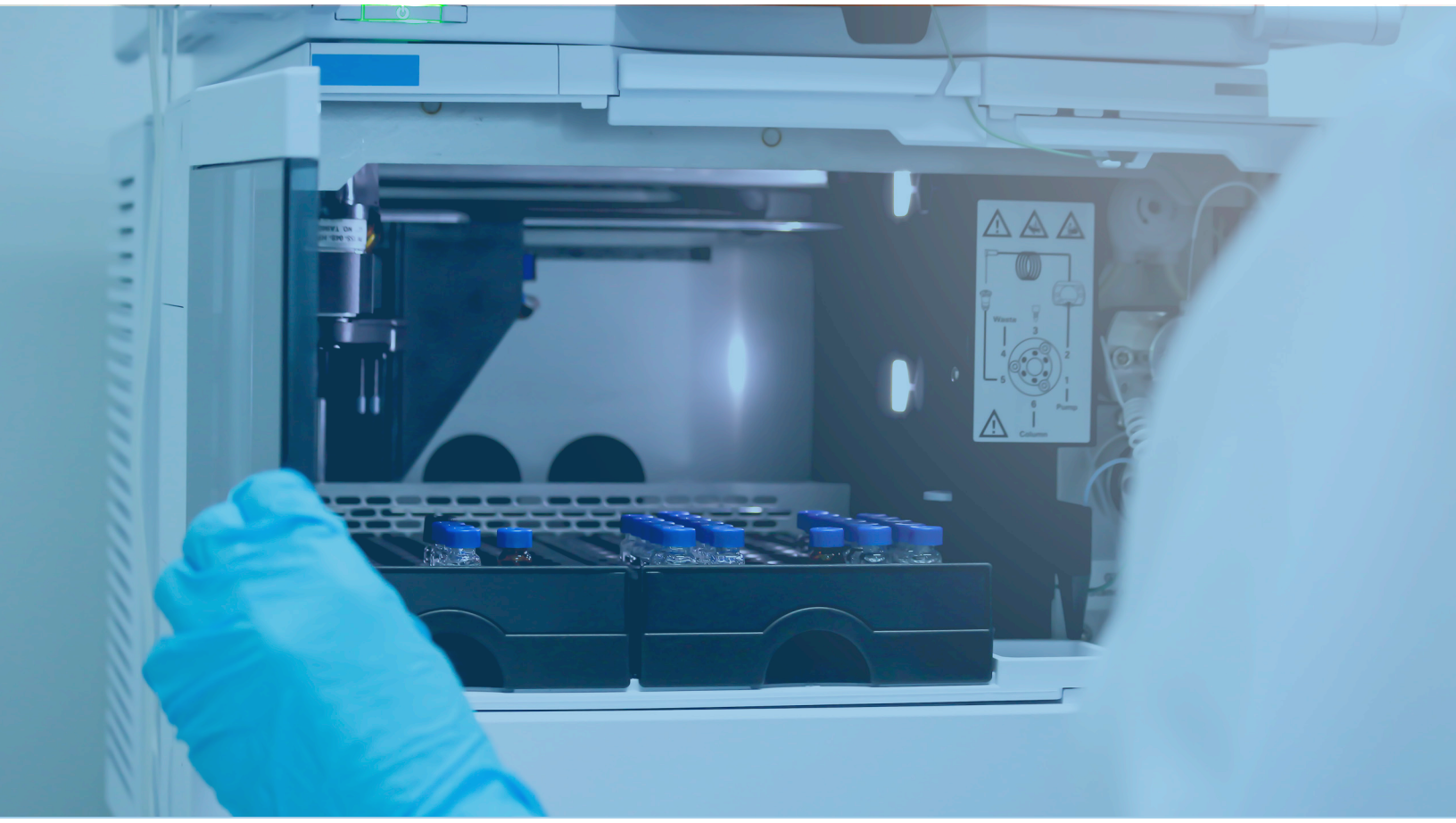
It is now much-discussed that the traditional approach of looking at purification and separation in terms of “size” can be reimagined based on “charge”. This means that operators/scientists can visualize mAbs as

positively charged while most of the contaminants, viruses, and cell/cell debris (due to the lipid bilayer and their phosphate groups) can be viewed as negatively charged.

Until recently, this approach was exploited on a limited basis. For example, improved consistency and predictability across different cell culture streams has been very well demonstrated by using a traditional approach (centrifugation or depth filter) combined with a chromatography platform such as 3M™ Emphaze™ AEX Hybrid Purifier.

In the long run, chromatography’s ability to advance single stage clarification platforms capable of removing all contaminants with “charge” will support biopharmaceutical industry’s move into compact flow through single use clarification and polishing trains.

As cell line development and cell culture engineering continues to accelerate, so do the opportunities to enrich discovery, clinical and manufacturing programs with innovative clarification technologies. To capitalize on this potential, there are certain key steps biopharmaceutical companies can take to evaluate the relevance of fiber chromatography technologies such as 3M™ Harvest RC and build the competencies required to leverage them to best effect.



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