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MICROBIAL SOLUTIONS - CELSIS®

Extending Column Resin Life and Reducing Downstream Costs through Rapid Microbial Methods

Key Points:

- Optimization of column chromatographic resin can provide significant process and financial benefits due to the high cost of chromatography materials and potential to degrade over time.
- Rapid microbiology can help maximize resin shelf-life and improve a manufacturing facility's ability to limit the impact of contamination.
- Current contamination control strategies depend on sanitization processes that degrade chromatography resins over time and traditional bioburden testing that require lengthy incubation periods.
- Rapid microbial methods can detect and control contamination sooner, providing manufacturers with additional benefits to downstream process efficiency and cost savings.

The Challenge

The benefits of faster quality control results are well known to most manufacturers when obtaining bioburden results sooner, allowing production to mitigate risk. Yet, many manufacturers have not found ways to extend the benefits beyond just production control to a point where they are creating production efficiencies. One of the potential ways that a company can mitigate costs and risks and extend chromatography resin utilization is by detecting and controlling bioburden contamination faster.

Affinity capture chromatography, utilizing resin, is a common early processing step used in biopharmaceutical processing. Critical in the overall production yield, this step ensures production impurities are removed from the product for further processing. Even with the purchase of standard resin materials, not accounting for specialized resin types, material and processing costs account for up to 10% of downstream production costs.[1] Therefore, manufacturers routinely reuse resin over multiple batches to amortize costs.

Unfortunately, costs aside, this is also a critical point where microbial contamination of the resin, its buffers, and column are possible and jeopardizes production.

Sanitization processes are typically optimized early in scale-up activities and are used to control contamination after and in between chromatography steps.[2] Appropriate sanitization must balance between effective microbial contamination removal and avoiding excessive degradation of costly chromatographic resin, which reduces its long-term usability.

Current methods to control routine process bioburden are sanitization cycles utilizing low concentrations of NaOH in NaCl-buffer solution, guanidine HCL in combination with acetic acid/benzyl alcohol, or acetic acid/ethanol.[3] Each sanitization solution has advantages and disadvantages when it comes to their effectiveness against certain contaminants, such as NaOH on *Bacillus spp*. Therefore, samples must be monitored closely for bioburden frequently, and rapidly, for both detection and identification.

This balance (and the long-term usability) is disrupted when microbial contamination is not controlled and companies must initiate remediation procedures, which can vary but commonly involve additional and more aggressive sanitization steps or discarding the resin altogether.

The table below highlights potential responsive actions performed due to a contamination event.

Potential Remediation Measures That May Be Taken on Detection of a Suspect Bioburden Event[3]
Apply a corrective sanitization using a more robust sanitization solution. MabSelect SuRe: 0.1–0.5 M NaOH; Prosep Ultra: 3% benzylalcohol (with 0.3% HCl). Acidification of the benzyl alcohol significantly improves the microbial kill kinetics, enabling effective sanitization.
Some companies perform proactive sanitization with a stronger solution following high-impact activities (e.g., after packing and prior to each batch).
Repeated sanitizations (e.g., three consecutive) may be more effective than a stronger solution in some cases.
Physical removal may be more important to remove spore-formers (higher caustic levels may not be effective in isolation).
Increase the flush volume and sanitize in up- and down-flow mode.
Empty columns can be passivated in response to detection of biofilm.
Preventative maintenance procedures and soft part inspection frequency is enhanced.
Manual cleaning of valves may be performed in difficult-to-clean locations.
Separate sampling of gradient cart and column rinse water generally demonstrates the contamination location at the column level.

Clearly, in order to avoid the need to add unnecessary remediation and further degrade resin materials, contamination must be controlled. Moreover, in order to avoid the non-forecasted expenses, production delays, or even shutdowns, potential contamination must be detected and confirmed as fast as possible. These factors have vastly greater impacts to an organization's bottom line, outweighing the day-to-day utilization improvements that have been developed.

While most production engineers have put much work into making resin utilization and production processes more efficient, production groups still rely on their quality control and microbiology departments to accurately detect contamination. Unfortunately, many of these labs still use traditional incubation methods based on enumeration, although faster methods exist. The fastest of these methods deliver a "yes/no" result to detect the presence of any contamination, which are not even considered, despite the tremendous opportunity to streamline manufacturing and testing.

The Solution

Thinking pragmatically, there are critical points in the manufacturing process, especially around these potential chromatography steps, where a count is allowed, but not expected. In fact, a test result of anything but 0 CFU requires action. So, why is it that labs are waiting for a count of 0 CFU, when they could know days sooner?

Labs that have adopted these methods not only discover contamination days sooner, but can initiate a response days sooner, sparing production from loss of product, extra work, as well as reduced wear on costly production materials, such as chromatography resin.

Celsis® rapid microbial detection is a technology that can achieve these operational and financial benefits by utilizing Celsis AMPiScreen® amplified ATP-bioluminescence to detect the presence of any microbial contamination in a sample. By streamlining testing down to the most critical question of whether the sample is contaminated or not, a confident screening assay will reduce a 3-5 day incubation period down to 1 day. By reducing every assay by 2 days, even without a contamination event, labs and production groups can take advantage of rapid results to champion even greater efficiencies, optimization improvements, and most importantly, their organization's bottom line.

To learn more about Celsis® rapid detection, visit criver.com/Celsis

References:

1. Hernandez R. Achieving Cost-Effective Bioprocesses. http://www.biopharminternational.com/achieving-cost-effective-bioprocesses.

2. Sargent B. Bioburden Contamination in Downstream Bioprocesses – Potential entry points for contamination and innovative solutions. Downstream Column. https://downstreamcolumn.com/downstream-bioprocessing/bioburden-contamination-downstream-bioprocesses-potential-entry-points-contamination-innovative-solutions/. Published August 23, 2017.

3. Murphy M, Bell BL, Moshi J, et al. Microbiological Control for Affinity Capture Chromatography Processing: An Industry Perspective. PDA J Pharm Sci Technol. 2018;72(2):213-221. doi:10.5731/pdajpst.2017.008045.

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