The Science Advisory Board

Bioprocessing in 2019 (What's Working and What's Not)

Featured Series

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The Science Advisory Board
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Executive Summary

The Science Advisory Board is pleased to present a compilation of articles originally shared on our website as a featured series focused on bioprocessing industry. The series is authored by esteemed science writer, Angelo DePalma.

The first article titled "*Extractables and Leachables in Single-Use Bioprocessing*" discusses the implications of these materials on human health and efficacy of pharmaceuticals. The second piece, "*Trends in Bioprocess: Continuous Upstream Bioprocessing*" address the concerns of a risk adverse pharmaceutical industry. The uncertainty and concerns with new technologies, scalability limitations, and financial feasibility in the context of current regulatory schemes are explored in the final editorial in the series, "*Trends in Bioprocessing: Why Not?*"

The Science Advisory Board is an international community of active researchers focused in the life sciences industry. The site provides current industry and research news, as well as insights into the technologies that drive innovation.

Extractables and Leachables in Single-Use Bioprocessing

By: Angelo DePalma

Single-use or disposable biomanufacturing replaces stainless steel tanks, bioreactors, and plumbing with plastic, to provide flexibility, agility, and speed to the production of therapeutic proteins. A recent market study estimates demand for Single Use Upstream Processing to grow at up to 15% per year through 2021, when demand will reach $3.7 billion.

As disposable processing worked its way from less critical steps (e.g. media and buffer storage) to more critical unit operations (cell culture, filtration), extractables and leachables (E&L) became a cause of concern. Leachables are chemicals that migrate from the single-use container into the process solution during normal use. Extractables, a subset of leachables, are found when single-use equipment undergoes heating or contact with solvents.

Just as consumers are concerned about chemicals from plastic packaging entering their food, biomanufacturers worry about the effects of E&L on patient health. E&Ls may interact unfavorably with, or even neutralize, biopharmaceuticals, thus rendering medicines ineffective. Moreover, the toxicology of plasticizers, slip agents, surface enhancers, monomers, and initiators normally found in plastics opens up a closet of unknown, potential health effects.

E&Ls affect the health of cultured cells as well. A study by Amgen scientists confirming that a common anti-oxidant additive to plastics inhibits cell growth is just one of many such investigations. For a fanatically risk-averse industry like biotech cell toxicity, the potential for human toxicology, and the prospect of falling out of compliance suffice to warrant action.

As the senior expert on E&L at Nelson Laboratories, Matthew Jorgenson, Ph.D., oversees the design of E&L studies in a dynamic regulatory and competitive environment. Nelson Labs also educates manufacturers and interacts with regulators on the science and regulation of E&Ls.

Nelson explains that over the last several years E&L testing has become significantly more complex and sophisticated. “Five years ago, an extractables study involving measurement of dried residuals by FTIR only was considered acceptable. Today, methods once common only to pharmaceutical work have been streamlined and applied more universally to medical devices and single-use biomanufacturing devices.” Today, extractables studies involve the use of multiple solvents plus analysis for metals, volatile organics, semi-volatile organics, and non-volatile organics using chromatography and mass-spectroscopy. (*continued on pg. 4*)

(*continued from pg. 3*) "The application of chemistry, vs. biological, data to make determinations regarding the use of devices and patient safety is relatively new. In vivo and in vitro biological tests, for example modified Eagles medium (MEM) elution for cytotoxicity, and chromosomal aberration for genotoxicity, have traditionally dominated the evaluation."

Manufacturers and regulators now accept that chemistry tests provide more detailed and better-predictive data for systemic toxicological effects of E&Ls than biological testing. The evolution of these tests has been rapid as the adoption of single-use bioprocessing continues.

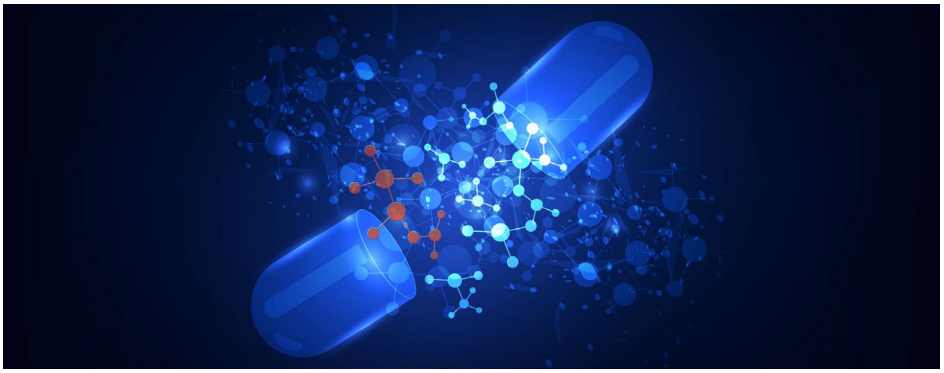
Single-use bioprocessing equipment uses biocompatible plastics as materials of construction. , which have a history of safe use and regulatory acceptance via the medical device industry. Adapting these materials to single-use bioprocessing has proved to be more problematic than anticipated, and plastics manufacturers are unlikely to invent new materials specifically for bioprocessing any time soon.

Biocompatible plastics represent a tiny sliver of the overall plastics market, diminishing the motivation for raw material suppliers to accommodate the stricter standards of end material with reduced E&Ls," Jorgenson says.

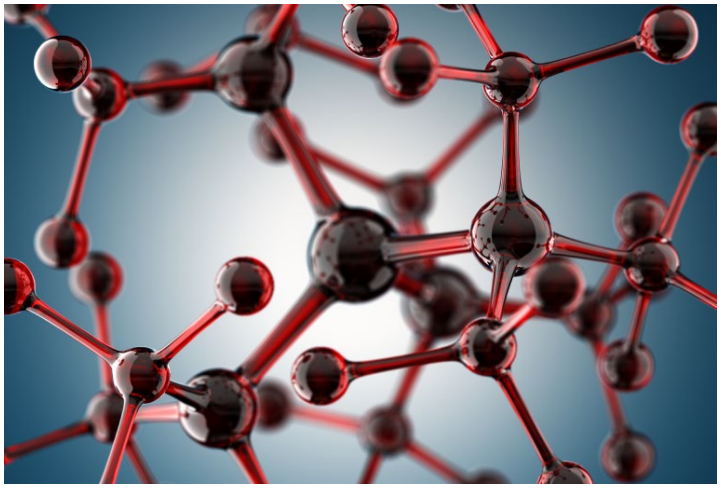
Instead, suppliers have focused on reducing E&Ls by employing higher-purity homopolymers (plastics consisting of a single subunit). "Part of the shift to low E&L-releasing plastics has been the increased use of chemistry testing in material evaluation and the upcoming enforcement of regulations requiring the use of CMR-free materials."

In this climate, where E&Ls will remain an accepted risk in single-use bioprocessing for the foreseeable future, the object is to characterize, understand, and control the implications of E&Ls rather than to eliminate them. Major stakeholders are therefore focusing efforts there, and on developing appropriate regulatory standards.

At the same time the regulatory landscape is changing rapidly. The recently released ISO 10993-1standard, for example, shifts the focus towards evaluation of single-use plastics using a risk-based approach to evaluating biocompatibility. "And the ISO 10993-18 standard, on 'chemical characterization of materials,' which is in the final revision stages, will dramatically update the current acceptable approaches to E&L," Jorgenson says. "There has been a lot of movement and feedback from the FDA regarding what they expect from these studies. Just within the last six months, our perception of what regulators expect in terms of E&L has changed quite significantly."



Trends in Bioprocessing: Continuous Upstream Bioprocessing



By: Angelo DePalma

Continuous manufacturing has greatly benefited consumer societies. Assembly lines are obvious examples for discrete manufacturing, while process industries rely on automation to transform raw materials into products continuously, without stopping even for the next process step.

For the expression of therapeutic proteins, continuous upstream processing involves culturing cells within a bioreactor based on hollow fiber or "perfusion" technology, that retains cells but allows protein products, waste, and small molecules to flow to a collection device, while media is constantly replenished. Perfusion cultures may continue for months instead of days or weeks with batch cultures, and easily achieve multiples of batch culture volumetric productivity.

Despite its high-technology reputation, the manufacture of therapeutic proteins is decades behind production systems for potato chips and cement in terms of continuous manufacturing and its essential component, real-time process analytics.

Why is this a subject of heated debate? Some experts believe that continuous cell culture is insufficiently robust to support the production of human drugs; others note that continuous processing is unsuited to large-scale single-use manufacturing, while still others claim that the regulatory and processing risks of perfusion cell culture makes it economically suspect.

Ron Rader, a respected industry observer from BioPlan Associates, has spoken with dozens of bioprocess experts about continuous upstream bioprocessing. From his perspective, adoption has reached a steady state, increasing slowly, but not for lack of interest. "Everybody wants perfusion cell culture, but they consider the technology as not fully ready for prime time."

As an example Rader notes that many of the world's leading biomanufacturers use Repligen's alternating tangential flow filtration (ATF, perfusion) bioreactor system. "However, it has been on the market for well over a decade and recently have sales topped $10 million, a rather small market for bioprocessing."

Companies are adopting perfusion for seed train intensification and early clinical scale production, but most will switch to batch processing, in stainless steel, for commercial manufacturing. "Perfusion remains most relevant at low-mid rather than large scales," Rader says. (*continued on pg. 6*)

(*continued from pg. 5*) "Larger perfusion systems are all custom manufactured, so scaling-up smaller, off-the-shelf systems can be a challenge."

The problem with current systems is bioreactor size in the age of single-use biomanufacturing. Other industry experts suggest that perfusion cell culture technology is not ready to handle the volume industry standard for single use production, currently between 1000 to 2000 liters. Perfusion systems, operate at 500 liters, but cannot compete economically to 2000 liter fed-batch processes. In this way, while it may seem logical that continuous upstream manufacturing will save money, for commercial purposes, this may not be true based on case studies and economic analysis.

Together, the regulatory risks associated with switching to less-familiar production technology, and the expertise required to operate such systems, pretty much seals the deal in favor of fed-batch cell culture in stainless steel tanks -- at least at large scale.

Continuous cell culture has its niche adherents. Molecules that lack stability during the two- to three-week batch fermentation might fare better in continuous mode because they are removed from the culture as they form. In those instances bioprocessors need to preserve and stabilize these products outside the bioreactor, until enough material is collected for the capture or initial ion exchange capture step. Perfusion mode may be a better fit for these molecules, especially in small batch settings. In this case, perfusion cell culture may be sufficient to meet market needs.

Despite its attractiveness, continuous upstream bioprocessing remains a "future" technology for routine biopharmaceutical production, despite the few widely publicized facilities running isolated unit operations in continuous mode. According to Rader leading companies are tackling such issues as integrating continuous with batch-processing unit operations, harmonizing continuous cell culture with single-use processing, and how to implement downstream continuous purification to match upstream productivity.

This way, when continuous cell culture is ready for prime time, they will be ready.

Bioprocess Innovation: Why not?

By: Angelo DePalma

Biotechnology and electronics are two high-tech industries that have delivered untold benefits to society. A different picture emerges on the production side. Where consumer product developers are more or less free to innovate, biotech relies on unit operations like fermentation, chromatography, and filtration which, although adapted for drug-making and optimized for yield, are essentially unchanged from decades ago.

Moore's Law still holds for electronics, as discovery-to-product life cycles constantly shrink through the combined effects of process innovation and competition. In biotechnology, competition is circumscribed by enormous entry costs, including those associated with regulatory compliance. Regulation plays a part in the introduction of phones and computer tablets, but product developers are not as constrained by human factors to the same extent as they are (and should be) for injected biopharmaceuticals.

Where discovery-to-product may be measured in weeks for consumer goods, for drugs the corresponding lag is years, sometimes decades, a fact that may be explained only partly by the seriousness of human safety.

These factors are why biopharmaceuticals will never be commodity products. Regulations governing every aspect of biopharmaceutical manufacturing assure that whenever a new production technology emerges, leading companies will take a close look and then, eventually, adopt the path of least resistance and stick with tried-and-true unit operations.

A literature search uncovers numerous innovations that could improve downstream efficiencies, to the point where purification platforms might handle even further titer enhancements. Among these are continuous chromatography, volume-independent depth filtration, alternatives to protein A capture, real-time process monitoring and control, and of course the expansion of single-use processing.

Yet despite these interesting science projects, given squeaky-tight development timelines and market dynamics few companies care to be the first to innovate, to step to the front lines of regulatory scrutiny and take a proverbial bullet for the team. (*continued on pg. 8*)

(*continued from pg. 7*) That is why cell culture (or fermentation), centrifugation, column chromatography, and filtration -- the four major upstream and downstream unit operations -- have evolved excruciatingly slowly. For example many processes now use fed-batch rather than simple batch culture, and depth filtration is replacing centrifugation for some processes. Drug sponsors and their suppliers will point to single-use manufacturing as a signature bioprocess innovation, but in reality all disposable process equipment achieves is to replace stainless steel tanks and tubing with plastic versions of exactly the same equipment. True, single-use has been transformative, but its utility is still moot for many processes, and its contribution to lower cost of goods is not always clear.

Reducing the cost of goods, the goal of any process improvement strategy, can be achieved in several ways. Substituting more-expensive reagents, buffers, media, and feeds with those that are more effective or less costly is one approach. Another involves optimizing utilization of such limited resources as time, equipment, and human capital. Most companies already have such programs in place. The third and potentially most effective way, process innovation, is a much less easily attainable goal.

In a recent Science Advisory Board survey, our members identified downstream operations in need of "technical innovation" outnumbered, by a factor of three to two, those who cited similar deficiencies upstream. One could make reasonable arguments for either position. But given the tenfold or greater (and still-ongoing) improvements in protein titers achieved through fed-batch cultures, and the persistent recognition of upstream-downstream capacity mismatches, not focusing on purification as a target for novel processing technologies would be like not thinking of a gorilla when commanded to.

Our respondents supported the idea that purification was in need of the most help, technologically speaking, through concrete examples. One, a QC scientist at a mid-sized biopharmaceutical company, noted that "changes in the regulatory framework affect innovation," but that companies might overcome these challenges through greater "interaction with the FDA." Compressing clinical development, he stressed (the second strategy mentioned above), is also possible through development of non-animal safety and efficacy assays to "reduce trial patient count and the time-to-market."

A second Science Advisory Board member who is a biotech industry manager noted that "adopting new technologies in biopharma always involves a great set of challenges," which bioprocessors can "overcome with effort." This engineer cited two unit ops, buffer dilution and cation exchange chromatography, which are used in nearly every bioprocess. The respondent's company recently instituted inline buffer dilution, and a switch from isocratic to linear gradient elution. Both innovations, despite their lack of earth-shattering impact on bioprocessing in general, involved a substantial learning curve.

A senior Science Advisory Board member is a general manager at one of Asia's leading biotech companies summed up the innovation conundrum most succinctly: "Innovation takes patience and time which, in today's competitive biotech marketplace, management doesn't have." Downstream process novelties, he said, are sorely (*continued on pg. 9*)

(*continued from pg. 8*) needed but the time and investment required discourages companies from trying, particularly when a less-than-optimized but perfectly serviceable process already exists. “Manufacturing teams are generally comfortable with existing processes, and fear the uncertainty of new technologies.”

Although no biotechnology company planning to remain in business will ever criticize the U.S. Food and Drug Administration, the idea that FDA regulations inhibit bioprocess innovation cannot be summarily dismissed. In its defense FDA has issued numerous guidances that encourage -- in the Agency’s inimitable style -- innovation, particularly in such areas as single-use, process monitoring, and overall modernization of production systems. Yet, in many aspects bioprocessing remains stuck in the past, and will remain so until the next biomanufacturing paradigm emerges.

About the Science Advisory Board

Established in 1997, The Science Advisory Board, a part of Science and Medicine Group, is an international community of science and medical experts. It connects a global network of research, development, and manufacturing professionals to collaborate on shaping the future of scientific technology. Members share their knowledge and experience with the community, advise and consult leading life science companies, and earn rewards for their engagement.