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Biomanufacturing, The 4th Decade: The Sky's the Limit

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As the biotechnology Industry enters its fourth decade, the business and technology dynamics are changing at a rapid pace. Innovation is driving new manufacturing technologies that improve efficiency, resulting in dynamic increases in process yields and utilization. More flexible, expeditious facility delivery platforms are resulting in significant improvements in project delivery times and capital cost reductions while provided significant new options for manufacturing biopharmaceuticals. New regulatory guidance emphasize the identification and management of risk in order to focus more on patient safety, resulting in a need for greater product and process knowledge and control be included in the design of the manufacturing facility.

A GLOBAL BUSINESS

Even as the global economy struggles to recover from the severe recession, the biotechnology industry continues to see growth from significant levels of research and development and to develop innovative technologies that are changing the manufacturing paradigm. Today we see an expanding global market where nations are earmarking significant levels of funding to develop and expand biomanufacturing capabilities.

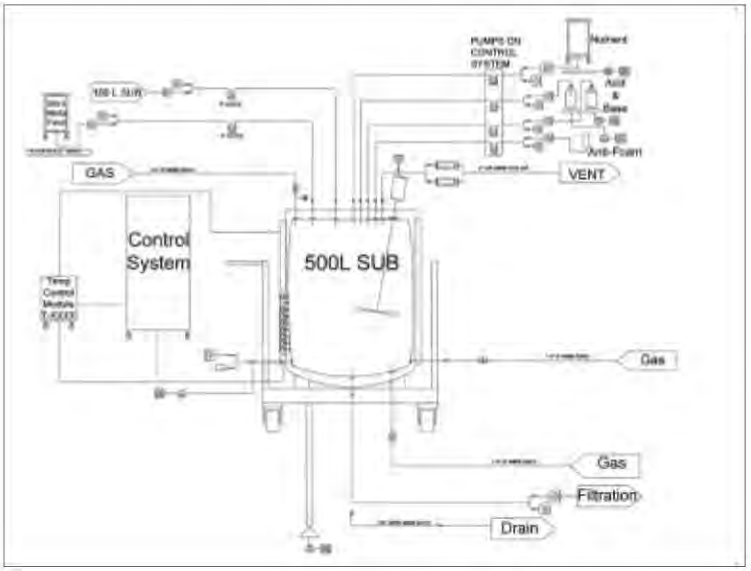
As the level of biomanufacturing capacity increases outside the US and European markets, companies are seeking new tools that will make the manufacture of both existing and new products more reliable in countries that once had no level of biomanufacturing capacity. Process development is focused on simplification of new and existing processes, using new technologies as the platform for change. This is resulting in the emergence of new biomanufacturing clusters across the globe.

TECHNOLOGY MARCHES ON

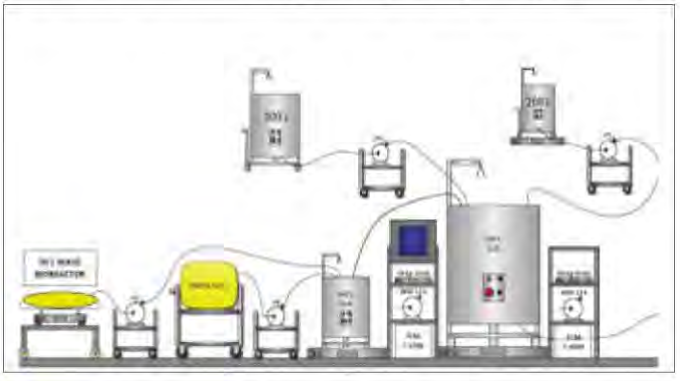
The evolution of biomanufacturing technology continues as companies develop the next generation of enabling technologies. As new regulatory guidance focuses on improved patient safety, platforms designed around Quality by Design concepts will become key tools in a company's drive to improved manufacturing quality and efficiency. The fast pace of advances in medical technology and the biosciences are driving both innovation and new product development. Advanced manufacturing business models that focus on rapid deployment and flexibility point to new manufacturing paradigms are being developed that require the technological advancements in order to operate effectively.

These technology advances include:

- Upstream Performance – Significant advances have been made in cell culture yields over the last two decades. Yields have increased from fractions of a gram/liter to upwards of 10 grams per liter (1). These increases have come through media optimization and improvements in cell lines. Improvements are expected to continue as Systems Biology and specialized artificial cell lines are developed with metabolisms modified to achieve specific performance goals. Harvest and recovery technologies will further improve the performance of upstream processes. In addition, various bioreactor options such as perfusion, attached, suspension, and micro carrier technologies are also likely to improve upstream performance and efficiency.
- Downstream Performance – While improvements in downstream processing lag behind advances in upstream processing, significant improvements in downstream processes are being observed. More selective capture steps using affinity chromato-



P&ID for a 500 L single-use bioreactor (SUB) system



Process flow diagram for single-use upstream cell culture process.

graph are possible along with the use of selective membranes and monolithic structured for Tangential Flow Filtration (TFF) processes. Advances may also be seen in non-chromatographic methods such as highly selective precipitation of protein specifics. Advances will also be seen in automated, multi-batch processes using smaller disposable columns.

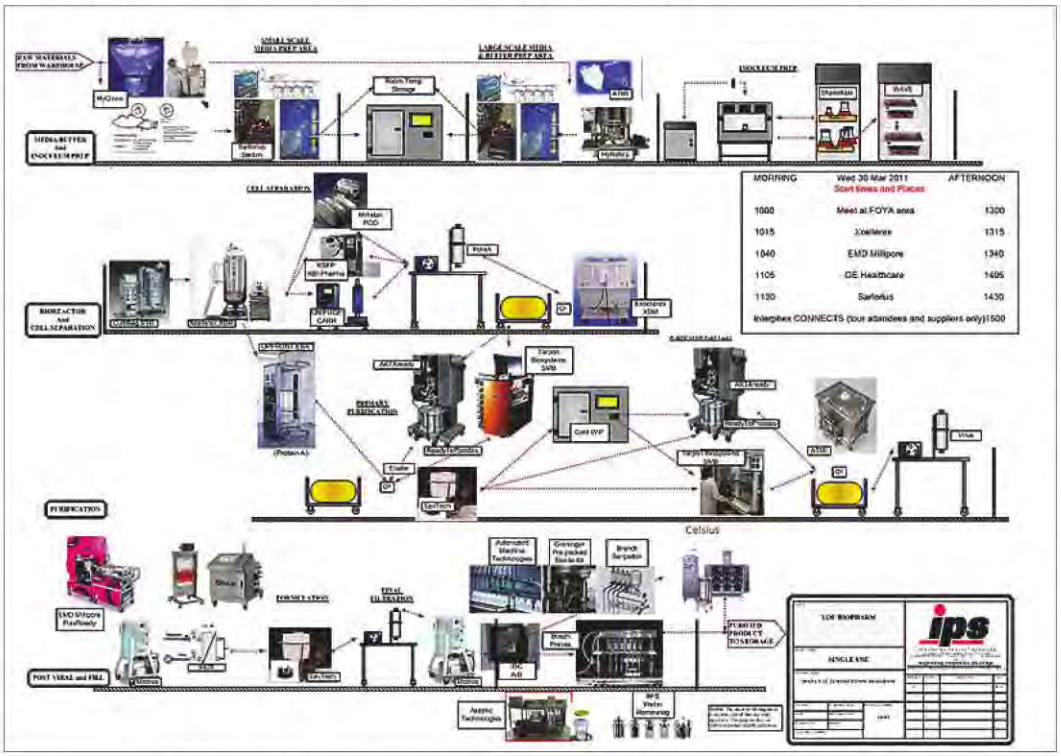
- Platform Technologies – As the industry's experience with manufacturing processes increases, platform technologies for a number of unit operations are being developed and marketed. These platform technologies, some based on well developed proprietary technology, will provide significant enablers for future improvements. Notable platform technologies are being seen in cell/bioreactor systems and purification platforms.
- Process Equipment – Advancements are being seen in equipment and equipment components unlike any time in the past decade. In particular, the increase in single-use systems (SUS) or disposable components are being developed and implemented in a much broader range than ever before. SUS provide a significant advantage in reducing cleaning, sanitization, and sterilization development and validation requirements. SUS also provide significant opportunities to isolate the process from the surrounding environment enabling a wide variety of opportunities in facility and process designs. In addition, advances in equipment designs in bioreactor configurations, centrifuges, and TFF units, are enabling a variety of process and facility modifications that enhance flexibility and improve utilization.
- Automated Systems – A wide variety of software and support hardware systems are becoming available to implement improvements in infrastructure systems. These include Manufacturing Executions Systems (MES), Electronic Batch Records (EBR), and Laboratory Information Management Systems (LIMS) to name a few. These computer technologies enable many significant enhancements to the drivers and reduce risk uncertainty.
- Single-use manufacturing systems continue to make their presence felt in preclinical and clinical manufacturing. Their increased use in commercial scale manufacturing, while still small compared to traditional stainless-steel based systems, is leading to the advancement of new hybrid facility models that will change the way companies repurpose existing capital assets for use in the coming decade. With these advances will also come the challenge of standardization while addressing risk to the product during manufacturing. System closure and equipment reliability will continue to improve. Novel platform technologies for products such as vaccines will reduce costs while increasing availability of therapeutics to a wider population.

DELIVERY REVOLUTION

Time is money. Speed is necessary to address demand. The Facility of the Future is now the Facility of Today. Flexibility, adaptability, and clonability are now necessities, not futuristic ideas that were once limited by the design and construction of manufacturing facilities. The Biomanufacturing Industry of 2013 is a different animal than it was 30 years ago. The integration of technology into defining facility attributes to produce advanced project delivery solutions relies heavily on technology that was non-existent just five years ago.

A number of facility design options are being discussed in different global industry forums. A variety of facility design and layout options are now possible that improve adaptability and flexibility. These in include processes that share common space in a "ballroom" or large general operating areas and more segregated, "matrix" approaches.

In addition, modular construction techniques exist for building facility components remotely and assembling them on-side in near "ready to go" modules. These modules can contain integrated HVAC systems allowing a variety of possible area classification options. Preassembled panels and components can be used to provide cleanrooms facilities that can be configured and reconfigured to address different process requirements. All of these different techniques provide improved cost savings and installation flexibility during the construction phase of a project.



Pictorial representation of some of the single-use equipment options that are available.

The Biomanufacturing Tour at InterPhex 2013 will include many of the companies that are developing the tools and equipment that will lead the advancement of the Biomanufacturing Industry in the coming decade. Key unit operations in both upstream and downstream manufacturing will be on display. The tour will provide attendees the opportunity to learn more about how these technologies are changing the manufacturing paradigm of today that will lead to unlimited opportunities for improvement tomorrow.

The companies that are part of this paradigm shift will provide Subject Matter Experts to both present their technology advances and answer questions from attendees. This event has been designed to be both informative and interactive. These companies include Sartorius Stedim, GE Healthcare, Pall Life Sciences, Applikon Biotechnology, EMD Millipore, and Thermo Fisher Scientific.