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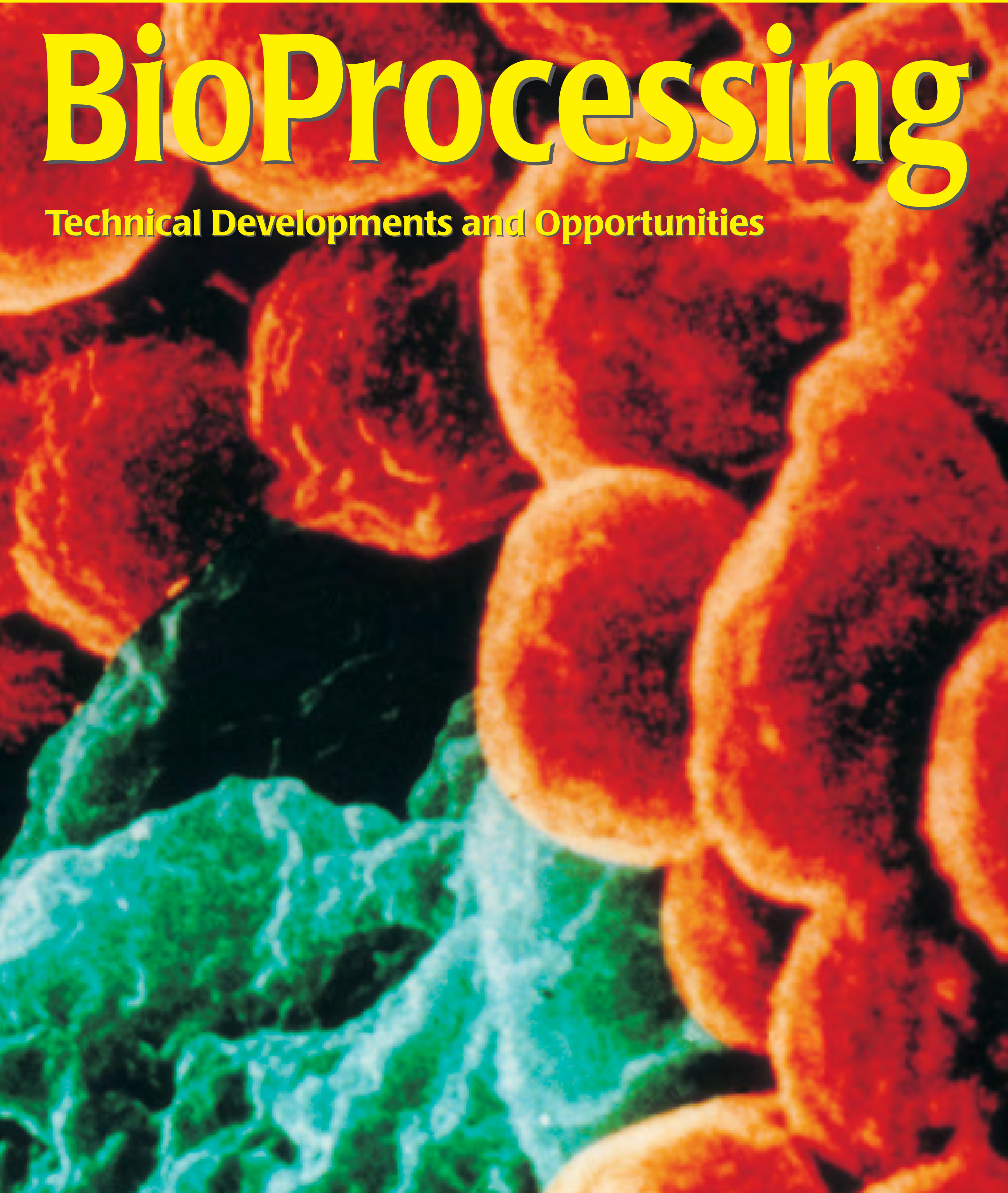
Technical Developments and Opportunities



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Industry Observations and Perspectives Part I

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Over the last seven years, The Williamsburg BioProcessing Foundation has held more than 30 conferences. Each of the eight annual meetings focuses on a highly specific area of biological process development and production, and involves many of the most knowledgeable people in each of the applications and technologies covered. The following reflects the opinions and perspectives developed while organizing and moderating these meetings.

Baculovirus and Insect Cell Culture

Baculovirus expression technology, or BEVS, gained its first broad industry exposure in the early 1980s, primarily through the many papers published by students and post-doctoral fellows in Dr. Max Summers' laboratory at Texas A&M University (College Station, Texas). This technology fostered popular appeal because of its simplicity and high protein expression capabilities. As more work was done, it became even more evident that this was a very rapid, and relatively inexpensive method for producing proteins.

It was also postulated that BEVS would offer a valuable means of producing recombinant proteins for use in human therapy, especially since baculovirus was considered non-infectious to human cells. It was thought that any problems with post-translational modifications of the manufactured proteins could be worked out, and fully functional glycoproteins could be manufactured.

Today, sound reasoning supports the science surrounding the glycosylation of the proteins that BEVS technology can generate, but no one has demonstrated these concepts at the pilot or production scales. As a result, BEVS technology has not been successfully used to produce a human therapeutic product. However, if an efficacious product could be developed, it is still believed that this production technology could result in products without the potential safety risks of materials manufactured with mammalian cells.

BEVS has been successfully adopted into a number of other applications where it is very practical. The most valuable applications appear to be those of rapid protein expression and production, where small amounts of a large number of proteins are needed quickly. Therefore, BEVS is used extensively to produce proteins for research applications, including the ever-expanding field of proteomics.

Furthermore, BEVS is very useful in producing protein fragments or antigens, for use in diagnostic kits, and thus has the potential for wide-scale use in vaccine applications. Numerous "sub-unit" vaccines are now being developed with BEVS technology, and several are working their way through clinical trials.

Still another valuable application is in the field of "biopesticides." Here, baculovirus is sprayed on plants, where it is consumed by insect larvae. The virus propagates in the larvae and is then released, as the insect dies, to infect more larvae.

BEVS technology is typically scaled-up in stirred-tank bioreactor systems, where it lends itself well to batch, fed batch, and perfusion modes of production and harvest operations. For certain applications, insect larvae are used as the bioreactors and produce virus at very high concentrations.

Monoclonal and Recombinant Antibodies

Being one of the earliest successful classes of biological products, monoclonal antibodies (Mab's) really helped the biotech industry get to where it is today. Certainly the broadest use of Mab's is still in in-vitro diagnostic kits. However, what really accelerated the growth of these products was their successful application to targeting or imaging, and drug agent delivery. Here, these proteins could perform valuable roles while not having to act as a fully functional therapeutic agent. These applications also allowed product sponsors to collect safety data for the injectable use of these molecules.

Initially produced in mice, and with hybridomas, a number of other production cell lines are used today for antibodies, including Chinese Hampster Ovary (CHO). When only a fragment of the antibody is needed, bacteria serve as a very economically attractive production alternative. In addition, numerous transgenic production techniques are being demonstrated including the use of sheep, goats, pigs, chicken eggs, insect larvae, and plants.

One of the more important developments in therapeutic antibody production is the ability to produce human proteins, either in human cells or the cells of other species. The use of human antibodies makes it far more feasible to pursue applications involving extended patient treatment with multiple product administrations. Now, there are far more applications to pursue with antibodies, and therefore more activity in research, development, and clinical studies.

Advanced analytical technology. However, the greatest impact on antibody and biological production has been the development of advanced analytical techniques and instrumentation. With today's technology, fully characterized molecules, and thus products, are a reality. Unthinkable seven years ago, sponsors are making process changes when products are in late-stage clinical trials, or even licensed production. Even more remarkable, host cell lines are being changed for products in late-stage development.

This increased analytical capability is resulting in more rapid, reproducible, and reliable data, and the ability to provide greater assurance that the products are identifiable, pure, and consistent. However, the concomitant increase of data submissions has raised the standards for all companies, and has heightened the expectations of those who must review and approve the products.

Experience gained through antibody production and licensing is now serving as a body of knowledge and precedence for the entire industry. Companies working on any type of biological product should attempt to capitalize on the lessons learned by this highly advanced industry segment.

Cellular Therapy

Cellular therapy comprises some of the more exciting and rapidly growing applications in the biological production industry. While we all remember the early work done with activated T cells, plus other limited cell-based therapies, there are now dozens of cell types and combination therapies being attempted at hundreds of sites throughout the world.

Applications can involve a single cell type, cells with a helper, or stimulating cell type, cells with "cocktails" of stimulating factors, and possibly even a gene vector. While most of the applications still involve the patient's own cells (autologous applications), it is hoped that more applications can be developed with a donor or universal cell line that can be used to treat a large population of patients (allogeneic applications).

Still other applications involve the use of cells from other species (xenogeneic applications), which introduce their own set of challenges. Recent successes in genetic engineering have helped to make cross-species cell use more plausible, and may even lead to the eventual production of complete human organs in other animals.

Without question, cellular therapy applications are some of the most technically challenging in the biological production industry. First, the cells must be collected from a clinical site without introducing contamination or resulting in an unacceptably heterogeneous population of cells. Then these cells must be processed under aseptic conditions while maintaining a high cell viability. Finally, the processed cells must be delivered to the patient in a clinical setting. Here,

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the processing entity, or product sponsor, can have little control over the timing and conditions for administration, or the techniques used.

Many problems persist with cell cryopreservation, and cell loss is often too high to consider such a storage step for the application. Therefore, most cellular therapies require that the cells be given to the patient within a few hours of their final preparation. Otherwise, the resulting cell viability will not be high enough and the treatment will have no chance of success. Without an opportunity to store the cells, typical product release testing cannot be accomplished. CBER (Center for Biologics Evaluation and Research) has been very accommodating in this regard, and has allowed cellular therapy products to be administered without the final product sterility testing that is required for essentially all other biologicals. As a compromise, in-process samples are tested for sterility, and gram staining is done on a sample of the final product. Procedures must also be in place to notify the doctor and patient if contamination is discovered with the longer-term sterility tests.

University challenges. Most of the cellular therapy applications are being conducted in university medical and research centers, where very little is typically known about current Good Manufacturing Practices (cGMP). There are so many processing facilities handling so many applications that CBER has little real chance of regulating them all. As CBER learns of new facilities, they are making every reasonable effort to interact with the key participants, and to arrange an inspection. However, many inspections can only be accomplished by FDA personnel who have very little experience with these complex processing applications.

Until recently, many processing centers have sought voluntary accreditation in lieu of FDA inspection. The Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) has played a vital role in providing facility audits, plus training on the basics of cGMP and Good Tissue Practices. However, such accreditation will not exempt a facility from CBER regulation, and sponsors will have to plan on becoming fully compliant with cGMPs.

Especially with these applications, CBER must be cautious that it does not infringe on "the practice of medicine." Cellular therapy, clinical care, research, and cell processing are often separated by particularly fine and fuzzy lines. The definition used to distinguish regulated products from those governed by the practice of medicine, is one of "significant processing." Here, this phase is intended to imply almost anything other than simply maintaining the cells, or as stated at a recent conference, significant processing could be interpreted as "doing anything interesting" with the cells.

Quality systems management is a major problem for these university-based centers. Manpower budgets are tight, and typically there is not enough activity to justify the development and staffing of an adequate quality system. Some facilities are able to share QA personnel with other functions within the university or hospital, but this is usually not a satisfactory solution.

Finally, the facilities needed for cell processing are quite specialized. A highly aseptic environment is required since it is difficult to avoid open manipulations in all the processing steps. Furthermore, the heavy concentration of autologous applications mandates that multiple batches must be processed simultaneously, and that the rooms and equipment must be amenable to easy cleaning and rapid "turn around" between runs. In addition, essentially all process contact components should be disposable. Then, when such facilities must be constructed in a limited space that is carved out of an existing university or hospital setting, the designers and operators are placed under especially difficult circumstances.

While encouraging data continues to be reported on a number of cellular therapy approaches, no applications or products have yet been licensed. Until a product is licensed, it will continue to be difficult for companies to raise the money needed to keep moving forward.

This is the first in a series of articles on the status of various technologies and applications in biological manufacturing.


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