Expanding Expression

Eric Langer at BioPlan Associates, Inc evaluates new biopharmaceutical expression systems, looking beyond CHO, E. coli and yeast

Nearly 55 per cent of biomanufacturing facilities today are actively considering alternative expression systems for products in R&D (1). By the time these products leave the development pipeline, there may well be far greater numbers of biopharmaceutical expression systems in commercial manufacturing than we have seen over the past 30 years. While there have been substantial improvements in the classic three expression systems (E. coli, CHO and yeast) over the years, until recently, there was a general lack of interest in adoption of newer platform technologies. The result is that nearly all biotherapeutic products manufactured today use the same familiar technologies.

The underlying reason for this stagnation has been the industry's inherent caution. "It is a conservative industry – nobody ever got fired for using E. coli, yeast or CHO," says Dr Tillman Gerngross, Currently Professor of Engineering at Dartmouth College. One reason for the slow adoption of expression system technologies in biomanufacturing is the regulated nature of the industry. Dr Gerngross has found that "making things cheaper while increasing regulatory risk has not been a winning formula in this industry: consider transgenic animals and plants."

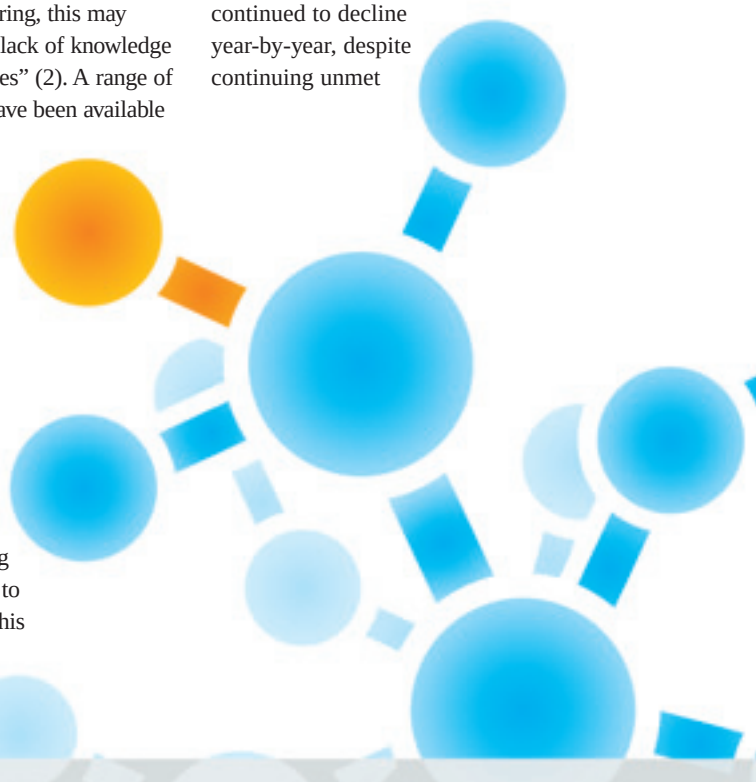
Cost saving is a relatively small part of the equation. Gerngross believes that new expression system technologies must improve product quality and have a direct therapeutic impact. Simply reducing costs is not enough: "Production costs are a small fraction of the final cost of goods – it roughly breaks down into one third production, one third purification and one third formulation and QC." Therefore, a protein cost-of-goods might be as low as four per cent, which means reducing production costs will not affect the overall cost structure.

THE NEED FOR NEW EXPRESSION SYSTEMS

Now, however, the need for innovation in the biopharmaceutical sector has taken on a greater urgency. According to Ronald Rader, author of the 'Biopharmaceutical Expression Systems' study, "High-tech industries adopt new technologies so they can produce better, cheaper and faster. Sticking with what you know may seem safe, but in biomanufacturing, this may have more to do with the lack of knowledge about emerging alternatives" (2). A range of promising technologies have been available for some years, but many companies continue to rely on outdated expression systems, which may compound the risks inherent to new drug development. This lack of forward thinking is having a stifling effect on biopharmaceutical manufacturing. In this increasingly competitive environment, companies are recognising that they may not be able to afford to continue along this path.

A DECADE OF DECLINE

Back in 2001, it was suggested that, for the industry to maintain even a modest growth rate, companies would need to triple the number of new molecular entities (NMEs) launched annually (3). Based on media releases from the top ten biopharma companies at that time, such targets appeared achievable (4, 5). However, new drug output has continued to decline year-by-year, despite continuing unmet



medical needs. Major companies have often publicised their commitment to innovation by highlighting their R&D, but several have struggled to launch even one NME in a given year. In contrast, much smaller biotech firms have frequently been able to outperform their larger counterparts. Many are now challenging the accepted wisdom that increasing R&D investment will automatically generate NMEs. This new view includes evaluation of novel expression systems.

BIOPHARMACEUTICAL INDUSTRY SEEKING BETTER PRODUCTS

As part of the '6th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production', critical concerns regarding the use of current expression systems were explored (1). In this survey of 443 biomanufacturers around the globe, 'yield/expression levels' was the single most critical concern regarding the use of current expression systems (indicated by 37.8 per cent of respondents, see Figure 1). This industry clearly appears to be asking for expression systems that perform better.

Interestingly, when asked about their single most important concern for their current expression system, less than two per cent of respondents indicated 'quality'. However, when making decisions on a new cell line or clone selection (see Figure 2), 'quality' was considered 'very important' by 70.9 per cent – though none directly defined 'quality'. Not surprisingly, 'yield' was indicated by 68 per cent of respondents as being 'very important'.

ADOPTION OF NEW EXPRESSION SYSTEM TECHNOLOGIES

The report also explored the potential for adoption of new expression systems (2). Fify-five per cent of respondents at biomanufacturing facilities indicated they would consider an alternative expression system in early R&D. However, 43 per cent of respondents in process development stages would consider alternative expression systems. This suggests that new drug product manufacturing technologies are not set in stone.

Figure 1: The most critical concerns regarding the use of current expression systems

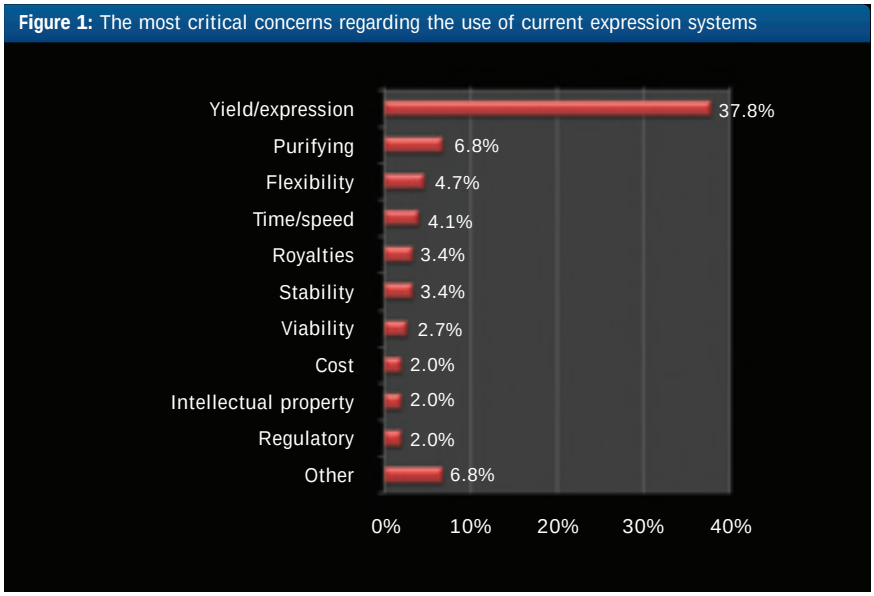
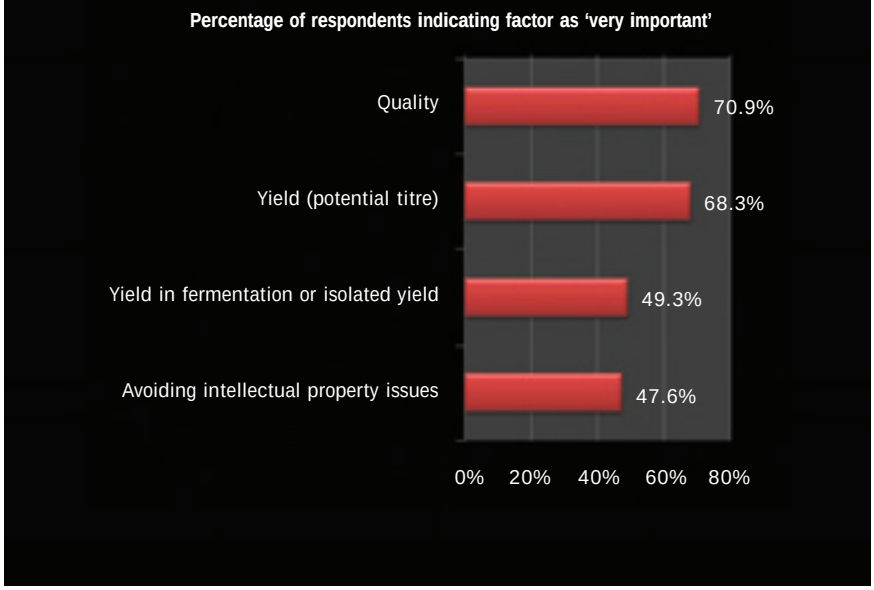


Figure 2: Importance of factors in cell line/clone selection process



Royalty payments for new expression system technologies were seen as much more acceptable to many biomanufacturers than might have been expected. The acceptance of new technologies seems to be dictated by how a new system would improve manufacturing. For example, nearly 46 per cent would pay royalties if the system offered greater yield, compared to 36 per cent if they were able to commercialise their 'failed' projects.

INNOVATION REQUIRES EARLY COMMITMENT

Despite the difficulties some companies are facing, there are substantial opportunities. Many new platforms exist featuring new host cells and organisms, but many managers in biopharmaceutical companies appear to have overlooked their sophistication and increasing availability (2). Of course, regulatory factors play a

major role here, as do issues surrounding intellectual property.

CLINICAL STRATEGY DRIVING NEW EXPRESSION SYSTEMS

It's not only manufacturing improvements that are driving the shift towards new expression systems. Many in the industry have seen trends toward the use of R&D strategy to improve a biopharmaceutical's clinical performance. For example, Patrick Lucy, Global Business Development Leader at Dowpharma's Pfenex business, feels that expression system platforms play a part in clinical strategy. Lucy believes that use of new prokaryotic expression platforms will increase due to their short cycle time in the fermenter and ease of genetic manipulation. He feels that biomanufacturers will shift for many reasons, one of which is that many companies have 'failed' products on the shelves that, "could and should be made more efficiently, and to higher clinical standards in newer expression systems."

Indeed, interest in new biopharmaceutical mammalian expression systems appears to be growing rapidly. According to Andrew Sandford, Vice President at Selexis, an expression systems platform company (Geneva), "Already, we have more than doubled the number of companies who have begun to actively change the way they plan their early development and manufacturing strategy. Many are...starting process development four to six months earlier."

NEWER EXPRESSION SYSTEMS IN COMMERCIAL MANUFACTURING

Use of newer expression systems is only just starting to become evident in terms of marketed products; for example, one insect cell/baculovirus-expressed human papillomavirus (HPV) vaccine from GlaxoSmithKline has received approval in Europe and is pending in the US, and Atryn, containing recombinant human antithrombin III made from the milk of genetically modified goats, has received approval both in the US and Europe. But looking over products in early development, one can see that newer and more diverse expression systems are finally being adopted. Many biopharmaceutical companies, particularly the larger, more successful ones, and large pharmaceutical companies who are becoming ever more involved in biopharmaceuticals, are now using multiple expression systems during early-phase product R&D, and then selecting the one that provides both optimal molecular characteristics and manufacturing options.

SELECTING OPTIMAL EXPRESSION SYSTEMS

One of the first decisions in biomanufacturing, of course, is to select a manufacturing expression system and associated upstream processing engineering. Probably the most important decision facing those planning to manufacture a candidate recombinant protein is whether to use well-established expression systems currently in place for most recombinant protein manufacture – notably E. coli, yeast and CHO cells – or a newer platform, which is perhaps better and more suited to specific needs. Use of multiple expression systems to make candidate products for early testing allows companies to select the product, expression system and associated up- and down-stream processing with the desired optimal properties, which will increase the likelihood of commercial success. With glycoproteins manufactured in eukaryotic cell culture in particular, the use of different host cells and associated expression systems results in products with different glycosylation and other structural properties, pharmacological activity and toxicity, including immunogenicity.

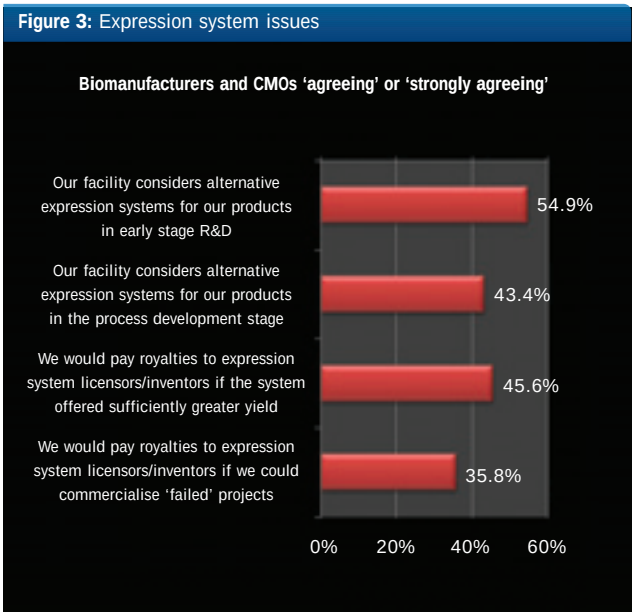
IMPORTANCE OF NEWER EXPRESSION TECHNOLOGIES

For an industry based on innovation, newer manufacturing technologies can be vital for a company's survival, and thus worth the expense, time and effort involved. Older technologies have the advantages of predictability and regulatory acceptance. But, considering that many of these technologies entail lost opportunities, as we move into the future, older technologies may find themselves increasingly limited by their performance.

Many new technologies offer much higher yields and numerous other advantages. With some expression systems now offering complex glycoprotein yields at over 30 grams/L, the cost savings compared to the 1.95g/l average industry yield using older technologies become clear (1).

Not all manufacturers wish to blaze the trail and be the first to seek regulatory approval. For those desiring to see validation by others in the industry, there are expression systems and genetic engineering technologies that have found well-known and aggressive licensors to provide safe choices. For example, the PER.C6 mammalian cell line-based expression system, the Pichia pastoris (yeast) expression system from Research Corporation Technologies (RCT); insect cell/baculovirus expression systems from various organisations, including Protein Sciences Corporation and Boyce Thomson Institute for Plant Research (Cornell University); the Glutamine Synthetase (GS) System from Lonza for optimal transformed cell selection and amplification; and His tags (poly-histidine fusion affinity tags) from Roche, have each already been licensed by 10s or, in some cases, even a 100 or more companies, including licenses for commercial-scale manufacture. For these and other technologies, manufacturing

Figure 3: Expression system issues



experience and regulatory filing-requisite data are generally already available and are often included in licensing packages, and one can choose from multiple CROs or CMOs with relevant experience who have already negotiated licenses for their contract manufacturing services.

A wide variety of bacterial hosts are available, including those such as Bacillus which are well-established for industrial chemical manufacture, and well-known but underused mammalian cell lines, including NS0 and HEK293 useful for antibody manufacture. There is also a large variety of other microbial, fungal, moss, algae, greenhouse and field plants, protozoa, transgenic animals and other transformable hosts, and even totally cell-free systems available for development and licensing. There are also wide varieties of promoters, chaperones, fusion affinity tags and other diverse genetic engineering add-ons that can substantially increase the yield, stability and simplify the purification of proteins expressed by almost any transformed host cells.

IMPACT ON BIOSIMILARS

With most biopharmaceuticals largely defined by their methods of manufacture, adopting a newer technology for a new product is one of the best methods to delay competition from biosimilars/FOBs and biogenerics. If one licenses and uses a technology covered by patents in relevant countries, this can provide a substantial barrier against biosimilar and biogenerics, particularly by opportunistic biogeneric copiers in international markets. Even higher levels and lengths of protection from biosimilar/biogeneric competition can be attained by using and licensing a patented or otherwise proprietary expression system that confers unique properties on expressed (glyco)proteins, making it much more difficult for anyone to copy your product.

WHAT IS A NEW EXPRESSION SYSTEM WORTH?

In the right circumstances, it could be worth billions in added profit, or it could make the difference between profit and loss and keeping others from copying the product. This is particularly true if your company can keep some key aspects of manufacture specific to the product (trade secrets) fully proprietary, not even disclosing them in patents. Otherwise, simply in terms of saving time and money in manufacturing a product on a large scale, it may be worth tens or hundreds of millions of dollars or, for major blockbusters, even more over the course of a product's lifetime. The increased yields, speed, adaptability, lower equipment costs, lower space requirements and other advantages offered by many newer technologies can mount up to provide considerable cost savings and profit.

Demonstrating the value of expression systems, particularly those that confer their own unique properties on resulting products, Merck acquired GlycoFi, paying over $400 million. Unlike many recent company acquisitions, GlycoFi's primary assets were its patents and know-how concerning mammalian-like glycosylation of expressed proteins in yeasts, not the few early-stage products it had in development. Recently, Merck announced that GlyoFi will be developing multiple biosimilar products using this technology, including a new version of Aranesp, Amgen's blockbuster second-generation improved version of its original erythropoietin (EPO) blockbuster. Even though potentially approved as a biosimilar, largely on the basis of comparison with Aranesp, this new product will be unique, an innovative product itself, and with its enabling, defining manufacturing technology fully owned by the company, Merck can expect significant protection from biosimilar and biogeneric competition for this product for quite some time.

Similarly, Hoffmann-La Roche Ltd acquired Therapeutic Human Polyclonals, a company that was developing methods for design and manufacture of both monoclonal and polyclonal antibodies in transgenic rabbits. Many companies, particularly larger ones, have taken options to license various expression systems while they continue to use and explore their potential. Also, indicative of the inroads novel expression systems are making into the mainstream biopharmaceutical industry, exemplified by the manufacture of biosimilars and biogenerics (involving emulating and copying old products), Genzyme recently announced it was developing multiple biosimilar products. In this case, Genzyme is apparently adopting transgenic technology primarily for the cost-savings it offers, rather than seeking to confer unique properties on manufactured products.

About the author

Eric S Langer is president at BioPlan Associates, Inc, a biotechnology and life sciences marketing research and publishing company in Rockville, Maryland. He has over 20 years' experience in biotechnology and life sciences management and market assessment. He is an experienced medical and biotechnology market publisher, practitioner strategist, researcher and science writer. He has held senior management and marketing positions at biopharmaceutical supply companies, and teaches biotechnology marketing, marketing management, services marketing, and bioscience communication at Johns Hopkins University and American University, among others. He is co-founder and Managing Partner at BioPlan Associates, Inc and has a degree in Chemistry from the University of Maryland and a Masters in International Business from American University. Email: elanger@bioplanassociates.com

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