



Expression Systems Royalties Battle

What are improved production and yield really worth?

Biopharmaceutical companies generally try to avoid the idea of paying royalties on novel technologies, including novel expression systems, in part because of the inability to predict revenue flow after a product is commercialized. But even when production costs could be significantly reduced, many remain hesitant. Despite this, adopting new technologies continues to be fundamental to improving product quality and cost.

According to Ronald Rader, author of the BioPlan Associates report, *Biopharmaceutical Expression Systems: Current and Future Manufacturing Platforms*,¹ “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.”

One reason for the limited adoption of expression system technologies in biomanufacturing is the conservative, regulated nature of the industry. Tillman Gerngross, PhD, professor of engineering at Dartmouth College, co-founder and CEO of Adimab Inc. (Lebanon, NH) and co-founder, and ex-CSO at GlycoFi,

which was recently sold to Merck & Co. (Whitehouse Station, NJ), has found that, “Making things cheaper while increasing regulatory risk has not been a winning formula in this industry; consider transgenic animals and plants.”

Rather, Gerngross believes adopting technologies that improve product quality in ways that have a direct therapeutic impact is where the greatest value is added. Improved expression systems must do more than simply reduce costs. “Production cost are



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a small fraction of the final cost of goods—it roughly breaks down into a 1/3 production, 1/3 purification, and 1/3 formulation and QC.” Therefore, a protein cost-of-goods might be as low as 4%, which means reducing production costs will not affect the overall cost structure. Which doesn’t leave much room for royalties to the supplier of such technologies.

ADOPTION OF NEW EXPRESSION SYSTEM TECHNOLOGIES

As part of our *Sixth Annual Report and Survey of Biopharmaceutical Manufacturing*, we explored the potential for adoption of new expression systems.² We were not surprised to find that 55% of respondents at biomanufacturing facilities indicated they would consider an alternative expression system in early R&D. However, we did find that 43% of respondents in process development stages would consider alternative expression systems. And this suggests that for new drug products, manufacturing technologies are not written in stone.

We also found that royalty payments for new expression system technologies were seen as much more acceptable to many biomanufacturers than we had expected. The acceptance of new technologies seems to be dictated by how

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a new system would improve manufacturing. For example, nearly 46% would pay royalties if the system offered greater yield, and 36% would pay royalties if they were able to commercialize their failed projects.

STICKING WITH OLD METHODS

The historical reasons that biopharmaceutical organizations are now primarily using the tried-and-true, common protein production expression systems stem from the industry's conservatism. Today, there is a need for increasing titers. Many believe that as long as the large numbers of current manufacturing projects using conventional expression systems continue to improve, the demand for novel systems will stagnate. Says Gerngross, "It is a conservative industry—nobody ever got fired for using *E. Coli*, yeast, or CHO." Many in the industry expect alternative expression systems to make strong headway, but only when they go beyond simply reducing costs, and provide such advantages as improved therapeutic properties.

LICENSE OR ACQUIRE

Pharmas requiring technology improvements may also consider company acquisition. In 2006, for example, Merck acquired GlycoFi for \$400 million to access their yeast glycoengineering and optimization technology. Their objective was to produce therapeutic proteins more effectively in *Pichia* (yeast) instead of Chinese hamster ovaries (CHO) or NS0 cells, offering improved speed and quality.

Such outright technology acquisitions can be cleaner than technology deals that involve some kind of risk-reward sharing over time, where both the product developer and the innovator company share the risk if product sales do not meet expectations.

Another concern with licensing and royalties is "royalty stacking". Though more common in drug product licensing, it is one of the risks technology adopters face. Royalty stacking is caused when multiple overlapping patents compel companies to obtain multiple licenses. Pharmaceutical companies are increasingly hesitant to

form alliances with biotechnology companies if potential royalty stacking issues exist.

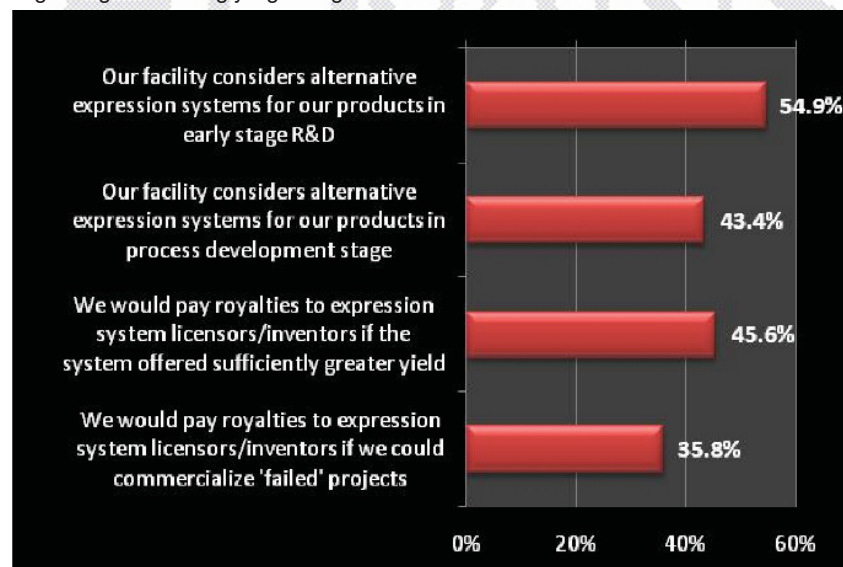
Information on alternative expression systems and genetic engineering technologies is readily available.¹ Most technologies can be licensed at reasonable fees for evaluation purposes, and most are available for commercial license on a nonexclusive basis. Some expression systems may be licensed exclusively, with this generally costing more than taking a nonexclusive license, but can provide assurance or insurance against your product competing with another similar one.

Although it increases costs through licensing fees and royalties based on annual product revenue and sales, technology licensing is often the only prudent option for most organizations. Licensing is the only legal and fair method of using technology developed by others, particularly if covered by patents. Most organizations, whether biopharmaceutical companies, CROs, CMOs, universities, or government laboratories, having invented and patented relevant technology invariably seek to license it out and get some return on their investment.

Licensor organizations generally will work with companies to tailor licenses to their needs. This may involve various combinations of up-front versus post-marketing fee arrangements. For example, a small company may prefer to pay a lower up-front licensing fee in return of somewhat higher royalty rates on eventually product sales. Those confident that a technology will be used to manufacture one or more products may prefer to pay higher up-front fees with lower back-end royalty rates. For major products, including blockbusters, this approach can save \$100s of millions over the course of a product's commercial life.

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Figure 1. Expression system issues: Biomanufacturers and CMOs "Agreeing" or "Strongly Agreeing"



Source: 6th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc. April 2009



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Many technology sources are receptive to providing a limited license for access and use of their technology for in-house evaluation purposes. Some companies and non-commercial organizations with expression systems in development may be very eager to collaborate with companies that will actually use their technology for product manufacture.

With the pharmaceutical industry being very conservative, and with companies and regulators having distinct preferences for proven, known technologies, those companies among the first to actually commercially manufacture a product using a newer technology can provide its developer with invaluable real-world cost-of-manufacture data and the references needed for wider commercialization of their new tech-

nologies. Thus, those among the first to license a new expression system or related genetic engineering technology can often receive better licensing terms, although the risk of failure or problems obviously increases with being among the first adopters.

Unlike licensing of actual product candidates, most licensing of process technology will be done in the relatively early stages of product development. With there being a large number of technologies available from many sources, there is more competition. This can tend to keep licensing terms down and increase the predictability of licensing terms and royalties associated with manufacturing technologies, compared to licensing of product candidates. Thus, in comparison with licensing of candidate products, licensing of manufacturing technologies tends to be more competitive and predictable

in terms of fees and royalties.

ARE NEWER TECHNOLOGIES WORTH THE COST?

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 advantages of predictability, and regulatory acceptance. But when 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. ♦

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2. Sixth Annual Report and Survey of Biopharmaceutical Manufacturing, 2008–2009. Rockville MD: BioPlan Associates, Inc.;2009.