gibco® by life technologies™

The next bioprocessing revolution

Functional additives: a significant value addition

Since the first large-scale bioprocessors started churning out cell culture–derived products more than two decades ago, manufacturers have been working towards more and more ambitious production goals. Advancements in this industry include the development and implementation of optimized cell lines, medium and feeding strategies, disposable culture vessels, and in-process monitoring instrumentation. Manufacturers striving for ever-increasing product yield have had to implement these technologies in ways that ensure regulatory standards are met and that product quality is uncompromised. Now that many bioproduction technologies and processes are reaching maturity, manufacturers are seeking out the next level of refinements.

The next stage in bioprocess refinement

Commonly seen in production processes is the failure of cell lines to sustain specific productivity throughout the manufacturing time course, with drops typically observed as the culture period progresses. Manufacturers have implemented a variety of strategies to achieve sustained productivity, including (1) selecting or engineering cell lines with better performance profiles, (2) use of culture vessels that allow very fine control of temperature, pressure, agitation, pH, and dissolved oxygen to maintain optimal conditions, and (3) measuring viable cell levels and various metabolites during culture in an effort to define corrective supplements and treatments that would increase cell densities and the amount of protein being produced without significantly increasing the levels of inhibitory factors [1,2].

While culture modulators such as high-pH, single-component additions and the addition of growth factors, hydrolysates, sodium butyrate, etc. can yield improved titers, there is some concern that these supplements:

- Pose additional safety risks to production staff
- May compromise the steady state of the bioreactor
- Could adversely affect the quality of the end product
- Could jeopardize the regulatory compliance of the process

For most established fed-batch processes, increases in productivity have been largely achieved through systematic optimization of media formulation and the development of feeding regimes that support higher cellular biomass and cell-specific production of the molecule of interest [2]. As an extension of successful fed-batch strategies (such as the use of matched media and feeds), the next stage in bioprocess refinement involves the development of highly concentrated functional additives that can be added to each bioreactor run in the smallest amount necessary to give good titer increases. Ideally, these functional additives would have neutral pH and be formulated using standard cell culture media components so that no additional risks to personnel, bioreactor steady state, or product quality would be imposed.

The ideal functional additive would have the following characteristics:

- Easy to use–neutral pH additive that is safe to handle and easy to implement in your process
- Trusted components—formulated using animal origin–free and chemically defined ingredients already in typical base media and feeds; poses no additional regulatory compliance complications
- Maintains bioreactor steady–state—highly concentrated additive allows targeted and titrated use so the smallest volume necessary is added to culture
- Cost/effective—potential to deliver sufficient increases in titer per run, so that the cost per gram is the same as or possibly lower than for your current fed-batch process

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Understand the real cost of a functional additive

Production cost is a major consideration for every manufacturer. An ideal functional additive such as the one proposed above might be expected to carry with it a high price per liter, but it is important to look past mere cost per liter when trying to assess cost-effectiveness. For example, increasing yield can have a dramatic effect on the cost/benefit calculation. For the sake of argument, let's say that a functional additive came on the market priced at $600/L, but only a small volume was needed to deliver double the titer compared to same bioreactor run without the additive. From the table below, using 300 mL of the functional additive in a 3 L culture increases the cost per run by $180, or 60%, which is significant. Taking into consideration the increase in titer, however (from 1 g/L to 2 g/L), the yield increases from 4.2 g to 9.0 g, or 114%. This makes the final cost per gram of product almost *$20 lower* when using the functional additive—a sound investment.

Also, a functional additive strategy such as the one described here would offer increased yield without capital investment or could allow your facility to reduce the number of runs per year on a particular product, freeing up capacity for other projects.

Table 1. Example calculation of bioprocess runs with and without a highly concentrated functional additive.

	Current process	Process including functional additive
Base medium	3 L at $60/L = $180	3 L at $60/L = $180
Feed	1.2 L at $100/L = $120	1.2 L at $100/L = $120
Functional additive	0	0.3 L at $600/L = $180
Total cost of the run	$300	$480
Yield	1 g/L in 4.2 L = 4.2 g	2 g/L in 4.5 L = 9.0 g
Cost per gram product	**$72.43/g**	**$53.34/g**

Calculate the benefit for your facility

Highly concentrated functional additives represent the next stage in the development of base media and feeding strategies for bioprocess facilities. When considering the additional cost associated with the use of a functional additive similar to that described here, it is important to look beyond the initial raw material costs per liter.

To help you with these calculations, we've developed a downloadable app that allows you to enter your current bioprocess parameters (including costs and yields) and compare them to the yield improvements you'd get using additives. Download the app today to see what the real cost/benefit data are.

Applications beyond titer

Although the example presented here focuses on the next way to improve titer, it is also possible to imagine other functional additives that would simplify regulatory pathways and reduce costs by enabling the modulation of product quality parameters. For example, if a functional additive led to increased therapeutic potency through glycosylation improvements, less product might be required per treatment, or more doses per run could be achieved (reducing the cost of goods in a different way). This means that the next wave of value-added products for biomanufacturing could be effective in very small amounts and still add significant value to your process stream.

For questions or more information about Gibco® product alternatives from Life Technologies, contact Mark Stramaglia at mark.stramaglia@lifetech.com or Peggy Lio at peggy.lio@lifetech.com, or go to lifetechnologies.com/FunctionMAX.

References

1. O'Callaghan PM, James DC (2008) Systems biotechnology of mammalian cell factories. *Brief Funct Genomic Proteomic* 7:95–110.
2. Li F, Vijayasankaran N, Shen AY (2010) Cell culture processes for monoclonal antibody production. *MAbs* 2:466–477.

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