Determining the Cost of Manufacturing a Biologic Product

Kevin M. Egan
President, Borealis Biotechnology
kegan@borealisbiotech.com

A biologics cost of goods analysis or specifically, the cost of manufacturing a unit of biological material for clinical trials and ultimately for the market is an important part of the overall analysis of product value. There are several components to determining an accurate and verifiable cost of goods. These include process performance parameters, facility operational limitations, the direct and indirect costs of manufacturing including labor and materials, facility overhead, and depreciation costs of facility and equipment.

Process Parameters

At a high level, process parameters include expression levels/product titers and overall recovery and purification yields. However, product losses are typically incurred upon harvest and consideration should also be given to reduction in material due to allotments for QC and other sampling. It is important also to include bioreactor size since lower productivity often occurs as the size of the bioreactor increases. Bigger is usually better however since the reduced number of batches (and resulting decrease in labor and materials costs and QA/QC costs) can easily offset lower expression levels. It is necessary to include the longest unit manufacturing time in the calculations since this will directly affect throughput.

Operational Parameters

Often overlooked in the cost calculation are the operational limitations of the facility. Many people wrongly assume that a facility can be operated at close to 100% of the theoretical capacity and use this in their planning. Since there are many factors involved in performing a successful manufacturing batch it would be unwise to assume that everything will be performed perfectly every time. And once time is lost it cannot be regained. Since even small errors can result in time delays it is prudent to incorporate these unplanned events into the overall cost model. Thus, effective facility capacity in the biopharma industry is typically assumed to be 85% of theoretical capacity. Tied closely to this is the batch success rate. The success rate will be low (~50%) early in development as scale-up procedures are being designed and tested and batch records are being written. As more experience is gained the success rate should improve dramatically. A good manufacturing organization should see success rates approaching 95%. If the effective

capacity is pushed higher than 85%, the success rate will inevitably decrease due to operator error or equipment malfunction. This is not to say that occasional short surges in productivity cannot be implemented to meet a corporate deadline. This should not be the practice however as mistakes including operator error will inevitably occur, equipment will malfunction simply because there is limited time for routine maintenance checks, or a batch will not pass a QA inspection.

All manufacturing facilities should plan for an annual stoppage for maintenance. While not shutting down parts or all of a facility for maintenance may increase productivity in a given time period it will eventually result in an unplanned halt to production during a critical campaign as equipment fails. Strategies to minimize the impact of a slowdown or stoppage in production include scheduling facility shutdowns during typically slow periods such as the end of the year holiday season. Some organizations institute rolling shutdowns where portions of the facility are closed for maintenance during selected periods throughout the year. This can minimize the down time but requires extensive planning and highly trained staff. In any event, the cost of goods model should include an annual period of no production. This period for many organizations is as long as four weeks.

Throughput

Maximum throughput calculations, that is, the maximum number of batches and maximum amount of product which can be produced per year should also consider the amount of time needed between batches to prepare for the next batch. This time may be short (1 -2 days) for manufacturing of a new batch of the same product. However, if a second product is to be manufactured in the facility, product changeover is longer (at least one week) and needs to be included in the model.

A simple calculation illustrates the error in not considering operational limitations in the throughput equation. Let's assume it takes 6 days to produce product in the bioreactor; 5 days to purify the product; 1 day to clean the production and purification suites to get ready to produce the next batch of the same product; and there is sufficient staff to operate the facility 7 days per week. This schedule allows for one batch per week under steady-state conditions and a theoretical maximum of 52 batches per year. However, once we include a four week annual maintenance shutdown, and performance at 85% of theoretical capacity, the annual production weeks (and # of batches) drop to 41 per year. With a 95% success rate only 39 successful batches will be performed which represents a 25% reduction in throughput compared to the theoretical capacity and a corresponding rise in the calculated cost of production.

Labor Costs

Labor costs should include both direct and indirect labor. Direct labor includes the cost of salaries, wages, and benefits for personnel who work directly on the manufactured product. These include upstream manufacturing and downstream purification personnel as well as anyone directly involved in buffer preparation and staging of raw materials for example. Indirect labor

includes the cost of salaries, wages, and benefits for personnel whose services are necessary for the manufacturing process but who are not directly involved in manufacturing activities. These likely include facilities/engineering personnel, and QC/QA staff. Models can be constructed which show the impact of additional personnel on overall costs as the scale is increased. Increased costs are easily offset by the increased productivity of running at larger scales and the percentage of labor costs compared to overall manufacturing costs decreases dramatically. Labor costs should be treated as fixed costs since it takes months and several at-scale batches to train personnel properly.

Materials Costs

Direct materials include any raw material that is directly consumed in the manufacturing process, is physically incorporated into the finished product, or can be traced to the product. Indirect materials would include anything else necessary to manufacture the product that is not incorporated into the product such as tubing, media bags, gowns, and pipettes. We have found in practice that the distinction between direct and indirect materials is not an important one. All such materials are incorporated into a Bill of Materials as required under Good Manufacturing Practices and this BOM will be the most accurate metric of cost of materials per batch. The most expensive raw materials by a large margin are the purification resins. Efforts need to be undertaken during development to maximize the resin capacity and to study resin reuse. The number of times a resin can be reused for a given product and process amortized over the number of batches which will be performed in a given time period will result in a substantial reduction in the overall materials cost per batch.

Overhead

All manufacturing costs that are neither labor nor materials costs are classified as overhead costs. These costs include utilities, leases, permits, insurance, taxes, waste disposal, maintenance and repairs, maintenance contracts, tools and supplies, training, outside testing, outsourcing, non-capital equipment, and depreciation of facility and equipment. We treat depreciation of facility and equipment as a separate cost driver since the list is extensive and the costs can be a very large component of overall manufacturing costs if the facility is recently constructed.

Cost Model

We have developed an accurate, comprehensive, and user-interactive biologics manufacturing cost model. The Excel model allows the user to easily input process and operational parameters in order to obtain an immediate determination of manufacturing costs. By entering estimated market demand data the model will also provide extensive information on the amount of product and doses required as well as information on the number of batches and time required to meet demand. A simplified model is available which allows for an infinite number of process and operational conditions to be tested for sensitivity analysis. The model can also be customized for your specific process and product by license from, or consultation with, Borealis Biotechnology, LLC. A Checklist for Cost of Goods Calculations is also available.