OPTIMIZING COST OF GOODS for Cell Therapy Manufacturing

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Facility design decisions made early in conceptual design can have a significant impact on the cost of goods sold (COGS) in the manufacture of autologous and allogeneic cell therapy products. Understanding the impact of a COGS analysis is an important aspect of the early-phase design process.

For most cell therapies, emphasis is placed on the cost of starting materials, the protection and control of the supply chain, and the efficiency of manufacturing to support rapid cell processing. These requirements are discussed in detail within the content of the *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs) Autologous Cell Therapy* [1]. Organizations beginning the journey into clinical manufacturing will focus on the key topics outlined in the guide's section on manufacturing, including process understanding around unit operations, equipment selection, and process control. But what about the COGS?

"The cost of any form of biologic product is weighed against its therapeutic benefit in its cost–benefit analysis. This assessment includes considering the relative costs of manufacturing. The affordability of many cell therapy products (CTPs) is often driven by factors related to development, clinical manufacturing logistics, and facility optimization. Since many CTP processes are not yet considered 'robust' due to their lack of manufacturing support data, the question around COGS sometimes is not given its appropriate emphasis during early-phase design activities" [2, 3].

"Specific factors to consider include analytical testing, operational attributes, product protection strategy, manufacturing logistics, and technology solutions" [3, 4]. A number of factors impact COGS, including direct costs (labor, materials, and sampling); indirect costs (operating costs, consumables, and testing); and amortization/depreciation costs (facilities, equipment, and third-party services). Addressing these factors can produce significant data options for consideration during conceptual design.

METHODOLOGY

"The design of a manufacturing process for any biopharmaceutical product involves a proven methodology that includes criteria such as operating costs, capital investment costs, and manufacturing reliability and efficiency. Developing COGS values that are specifically driven by the attributes of the process/facility relationship will focus on a set of inputs and outputs that have a direct day-to-day impact on operational costs and manufacturing efficiency" [3].

"The key is to have a tool that will provide the necessary data for evaluation while also making the data accessible during the design phase of the project. As design attributes change, so will the data. The tool should be user friendly and easy to implement" [3]. Figure 1 provides a visual example of how a decisional model can be created.

"The inputs required to evaluate manufacturing costs would include personnel requirements; unit operational data; batch size; operational scale; qualification data; and materials and consumables.

For early-phase design development, the focus is on defining the established fixed costs that can be supported with available data, including:

- Equipment sizing/vendor data: In the model process, all unit operations are performed in single-use components. This is driven by scale of operation, flexibility, and level of automation. For this model, unit operations are assumed to remain manual-focused during the clinical manufacturing phases, consistent with many operations producing chimeric antigen receptor T (CAR T) cell products today. Key information would include product protection via biosafety cabinet (BSC)/isolator; cell processing via cell enrichment and cell washing; concentration; filling; and cryo storage.



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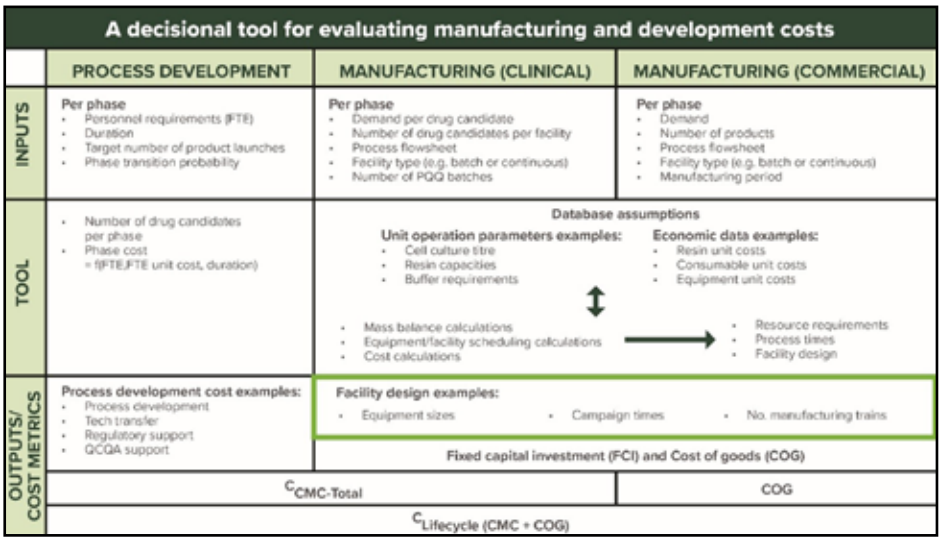
Figure 1: Sample decision model [5].



- Utility consumption: Load calculations based on facility attributes (heating, ventilation, and air conditioning unit sizing/zoning) and average energy cost (localized).
- Area sizing/classification: Energy usage intensity and operations schedule.
- Consumable costs based on target manufacturing outputs: Bags, micro beads, bottles, pipettes, and tubing.

There will also be a need to identify key assumptions necessary to complete the COGS model: batch targets based on manufacturing time durations; testing requirements; headcount, measured in full-time employees; energy costs; annual maintenance costs; and scaled facility costs (tax rates)" [3].

TOOLS

The tools that evaluate different production scenarios to aid in compiling costs depend on accurate data, or valid assumptions that cover the necessary cost model attributes. These tools can be either manual worksheets that use macros to automatically adjust data entry on a cell-by-cell basis in the spreadsheet or computer-generated models.

The key to success in generating numbers that have meaning and validity is the strength of the data input; "garbage in, garbage out" truly applies. Some examples:

- Equipment costs based on actual purchase price or validated bid price
- Accurate energy costs in dollars per kilowatt hour ($/kWh) based on actual monthly bills
- Mass balance volume accuracy for each unit operation
- Consumables costs: Equipment and personnel assigned units
- Sampling: Environmental monitoring and process costs and frequency
- Materials: Volume and cost per unit

Data entry must be specific and accurate. A worksheet tool would include items such as:

- Item type: Equipment type, price, and quantity
- Materials: A description of each line item
- Base UoM: The unit of measure for each item in the purchasing unit, e.g., ea. (each), L (liter), or g (gram)
- Purchase amount: Quantity purchased based on unit of measure
- Purchase price: Cost of each item purchased based on unit of measure
- Unit of measure quantity per patient: Quantity of the unit of measure used for each patient.

USE OF THE TOOL

To show the use of a tool focused on design input, a CAR T clinical/launch facility will be used as a model. In this basic model, the facility has the following set of operational attributes defined and included as factors during conceptual development: a focus on CAR T CTPs; phase 1, 2, and 3 clinical manufacturing; Grade A BSC in Grade B background classification basis for manufacturing; a 15-year amortization period; consistent average energy cost ($/kWh) for utility costs; and annual taxes and maintenance costs. A phased expansion approach to meet increasing manufacturing demands for clinicals will include manufacturing and support spaces. In phase 1, 15,000 sq. ft. will be used, followed by 45,000 sq. ft. in phase 2, and 90,000 sq. ft. in phase 3.

For the equipment platforms, the facility has the following set of operational attributes defined and included as factors during conceptual development: consistent unit operations through all phases of clinical manufacturing; equipment pricing based on current quotes within the last 12 months; operations classified as