A Right First Time Approach to Early Process Development

Dr. Linas Mockus, Allergan, Sr. Project Engineer, Mockus_Linas@allergan.com
Dr. Prabir Basu, Advanced Pharmaceutical Technology Institute, Managing Director, prabir1960@purdue.edu

ABSTRACT

In order to shorten the development time, it is important that resources in development be focused on doing things "Right the First Time". The cost of making a chemical compound that potentially has very attractive properties might be prohibitively high and finding a feasible alternative route quickly is imperative. History shows that even very promising drugs don't make to market because of their relative high costs of manufacturing. However, this may have been avoided if the researchers, early in Discovery or Development, could have identified the need for an alternative less expensive route.

In this paper, we describe a process evaluation methodology to be used either in Discovery or in Development during route selection or early process development. It is very important from business perspective to properly evaluate the process as early as possible and understand the impact of various factors and variables on the final cost of goods of the chemical. Selecting the best route early and employing valuable resources on the right steps of the chemical synthesis early can save company a significant amount of time and money.

INTRODUCTION

The cost of new drug development has soared to greater that $1 billion in recent years. At the same time, the number of new drugs submitted to the Food & Drug Administration (FDA) for approval has declined significantly. Some of the statistics are as follows:

- Of 5,000 to 10,000 screened compounds, only 250 enter pre-clinical testing.
- Of every 250 compounds entering pre-clinical testing, only one (1) compound is approved.
- Three of ten marketed drugs produce revenues that match or exceed R&D costs.
- It takes an average of 12-13 years from discovery of a new active ingredient until market commercialization.
- US pharmaceutical industry investment in R&D has increased from $1 billion in 1970 to an estimated $32 billion per year in 2002.
- The number of new chemical and biological entities launched has declined steadily over the years.

The numbers are staggering. It reflects vast amounts of resources being used to discover, develop, and market a few good drugs. Obviously, the pharmaceutical industry cannot afford to do this for much longer. The basic science for drug discovery and testing is quite advanced. However, the FDA rightly believes that the problem is that the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. There is a realization among the scientists in academia,

industry and the FDA that a paradigm shift is required regarding how drugs are discovered, developed, and manufactured. There is a famous Einstein quotation: “As long as we do the same things over and over, we cannot expect different results”.

Therefore, there is an urgent need for the industry to look at how the basic science is applied and investments need to be made to improve process and work efficiencies all through the drug discovery, development and manufacturing pipeline. Process development and manufacturing will have to play a strategic role in cost improvement and speed of bringing new drugs to the market.

There are many ways to tackle this problem. We propose to start thinking about possible costs associated with pilot scale or manufacturing at early stages of process development (or even discovery) so that there will be no surprises down the road. Today we are talking about Process Analytical Technology (PAT) and quality built in the process. Very often quality is associated with costs savings (for example, reduced solvent and associated solvent waste costs typically represent a more robust and environment friendly process).

When little or nothing is known about the costs of raw materials required for production of a certain chemical compound, a good & reliable estimate might be sufficient. This is true for new chemical entities that are manufactured from raw materials that are rarely used or used in small quantities. Estimating the costs of such raw materials for the scaled up version of the process (Cost of Goods or COGS model) constitutes the heart of this paper. The next step is a sensitivity analysis that helps to find those factors that have the biggest influence on the costs of the process. By comparing alternative routes, it is possible to establish the most attractive one at the very early stages of the process development.

In this paper, a tool that implements this methodology is described. The COGS model that is based on the cost data for several pharmaceutical sites is utilized in the development of this tool. It should be noted that the underlying COGS model might change in the different environment.

THE PROPOSED METHODOLOGY

We propose a multi-step procedure to estimate the costs of a scaled up process. Our assumption is that all routes are already identified.

- Develop a Cost of Goods (COGS) model from existing purchasing data. Typically, such data resides within SAP or some other ERP system. The model development is covered in the next section.
- Develop a Capacity Model for a given route. Capacity Model identifies the planned quantity of a chemical for each step (typically consisting of a single chemical reaction and separation). The planned quantity is the amount of the chemical we expect to be produced by the scaled up process. The characteristics of a process such as yield, excess amounts, and density are included in the Capacity Model. The Capacity Model also includes the characteristics of limiting equipment such as vessel size.
- Estimate the total costs (including labor) for this route.
- Perform sensitivity analysis to determine the key variables that influence the cost of making chemical (feed, batch time, yield, labor etc.).

- Perform a similar analysis for all routes.
- Choose the best route based on some predefined criteria (for example, minimal total cost under standard conditions with comfortable level of variability in total cost due to yield fluctuations). One or several backup routes should be chosen as well.

THE COST OF GOODS (COGS) MODEL

The COGS model is the key component of the proposed methodology. It estimates the cost of a raw materials needed for the selected route. The more precise the COGS model is the better estimate of total cost is achieved. In this paper, we will use the following COGS model:

$$\frac{\text{Unit Cost}}{\text{Aldrich Cost}} = e^{\alpha}\,\text{Planned Quantity}^{\beta},$$

where Unit Cost is the cost for one kg (l) of raw material at manufacturing scale while Aldrich Cost is the cost for 100 g (100 ml) of the same chemical; Planned Quantity is the amount of chemical (in kg or l) to be manufactured. It is obvious that ratio above should be non linear because of the economics for manufacturing large amounts.

It is worth noting that COGS model might have a different expression. However, the expression above was chosen to reflect the widely used formula for estimating the cost of equipment based on its volume. Since COGS model is derived from regressing particular chemical cost data to this cost function, it is important that representative chemicals from population are included in the sample. The cost function might be different for different types of chemicals (solids and liquids; with high Aldrich cost and low Aldrich cost; low, medium, and large quantities). It is possible that the cost data is rich enough to stratify the model further. COGS model as a side benefit gives a good estimate of the cost for a raw material. This might be a very important vehicle to negotiate the price when contracting the manufacture of a required raw material. Practice shows that for readily available commodity chemicals such an estimate is not necessary (and sometimes even misleading) but works very well for raw materials that are used rarely or in small quantities.

PROCESS EVALUATION TOOL

A tool was developed in order to implement the proposed methodology (1). Although simple, it had success by allowing quick estimates of the bulk park for the scaled up process costs and aiding with important go/not to go decisions. The tool was developed by using readily available software what made the tool even more attractive. It is based upon Excel (the de facto standard for engineering calculations) and Visio (for drawing process flowsheets). The capabilities and key elements of the process evaluation tool are depicted in Figure 1.

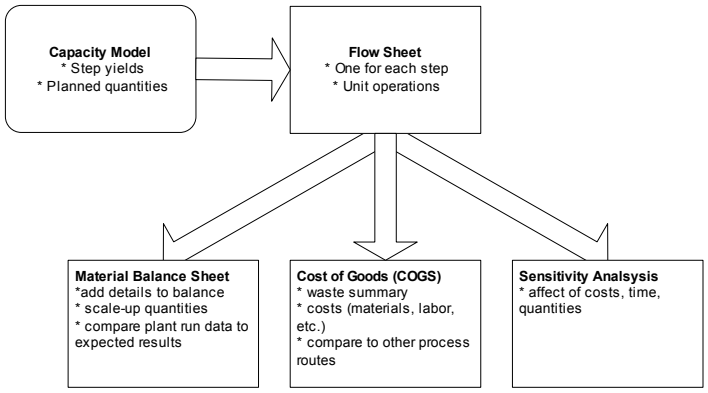

Figure 1. The capabilities and key elements of the process evaluation tool

	A	B	C	D	E	F	G	H	I
1	Dependent Steps								
2		Campaign	Excess	Weight	Capacity	Reactor	Number of	Batch Time	Total Run
3	Step #	Qty, Kg	Product, Kg	Yield	Gal/Kg	Size, Gal	Batches	Hr	Time, Hr
4	5	1,000.00		0.94	4.39	500	9	16.50	148.50
5	4	1,063.83		0.94	1.42	500	4	7.50	30.00

Figure 2. Example of a Capacity Model (Excel)

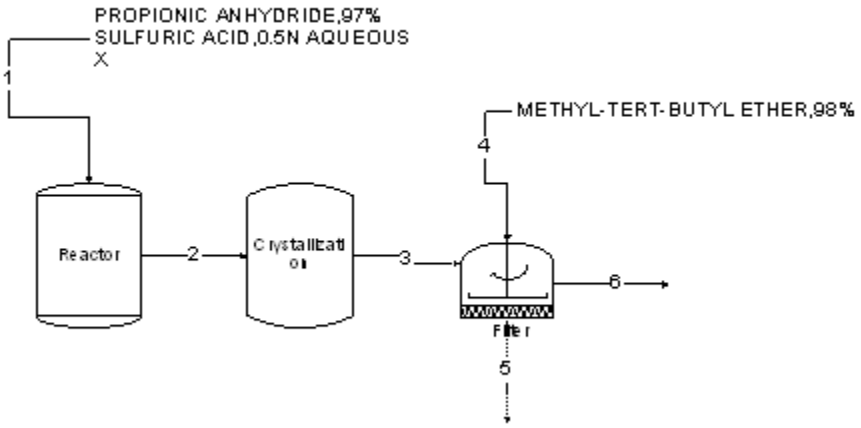

Figure 3. Example of a process flowsheet for a single step (embedded Visio object)

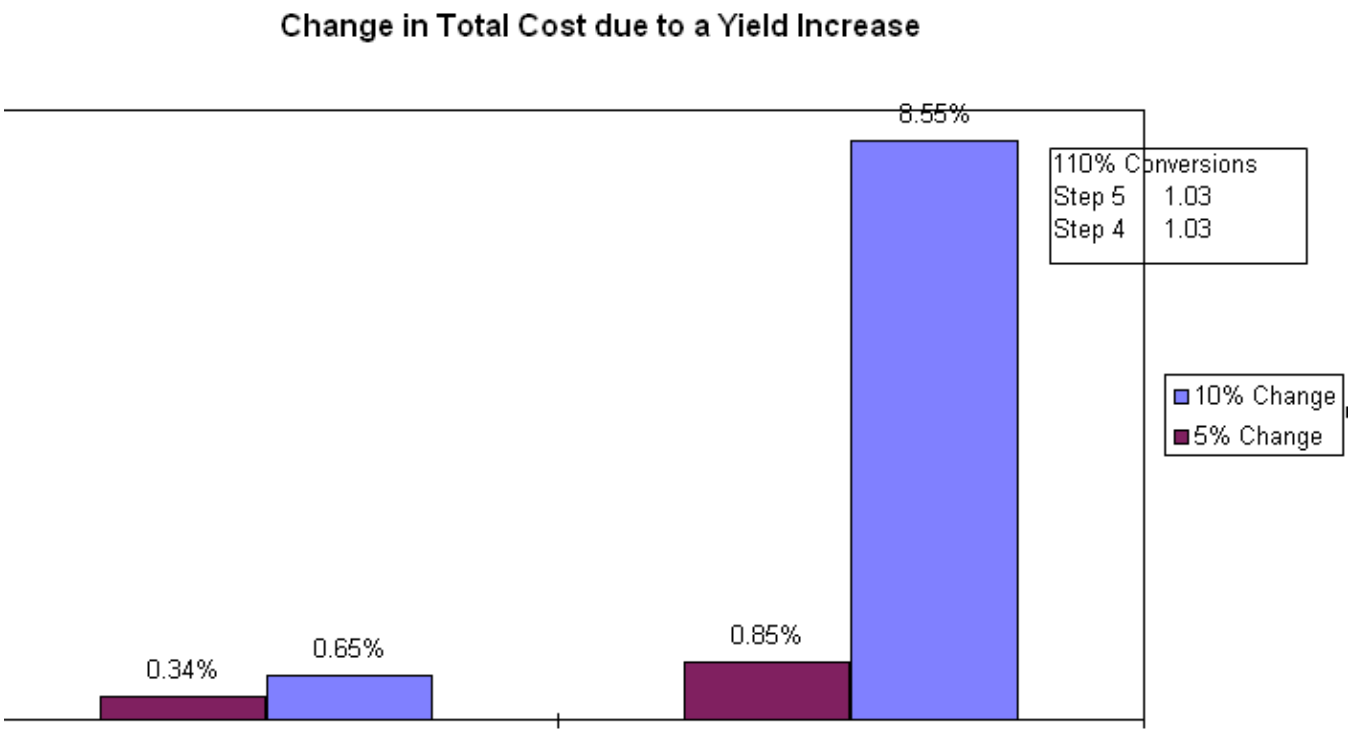

Figure 4. Example of a sensitivity analysis on yield (Excel)

CONCLUSION

The methodology to choose the best process routes is presented. In order to be competitive industry has to do things “Right the First Time” and the approach presented in the paper aids with this. Because of limited resources it is important that only right processes (both from therapeutic and economic aspect) move into pipeline. By achieving this industry can stop the steady decline in the number of new chemical and biological entities launched. It is imperative to embrace the technology advances and implement those in practice of early and late drug development.

REFERENCES

1. PAT: Process Assessment Tool, C. Seymour, B. Houston, J. Vinson, R. Mack, P. Basu, AIChE Spring Meeting, paper 122b (1998).