Integrating Design and Control with Six-Sigma for Bioprocessing Applications

Eyal Dassau and Daniel R. Lewin*, PSE Research Group, Technion IIT, Haifa, Israel

Extended Abstract

With worldwide revenues in excess of $400 billion in 2003, it is not surprising that the pharmaceutical industry can justify the investment of up to $ 800 million in the development of a new drug [1, 2]. However, with the main focus being on reducing time-to-market, the industry commonly relies on poor operating practice with regards to production losses, with low sigma-levels in the range 2-3 being commonplace, equivalent to production losses of as much as 35% due to off-quality products. Clearly, a direct consequence of each percent increase in acceptable production has a potential annual benefit of some $ 4 billion. It is also self-evident that a pharmaceutical process whose sigma-level is improved will also exhibit reduced cycle times, and increased overall efficiency and quality [3]. These commendable objectives can be achieved using a proposed novel approach, shown schematically in Figure 1, which combines:

a) *Process Analytical Technologies* (PAT), for data extraction, involving instrumentation as simple as a temperature indicator to more complex ones such as NIR or in-line HPLC. The ability of these devices to perform data acquisition and data-transfer in real time are vital to enable process improvements;

b) *Six-sigma methodology* (6σ), which serves as the driving force for continuous improvement by identifying the root cause or causes of low process yield;

c) *Process modeling*, based on systems biology and first principles models, which provide a basis for model-based control;

d) *Advanced process control* (APC), which serves as a high-level control system tier that can coordinate the operation of cascaded, lower-level controllers, to provide optimized regulatory performance;

e) *Statistical process control* (SPC), which serves as a safety net for the APC, and as a preliminary stage in the 6σ methodology.

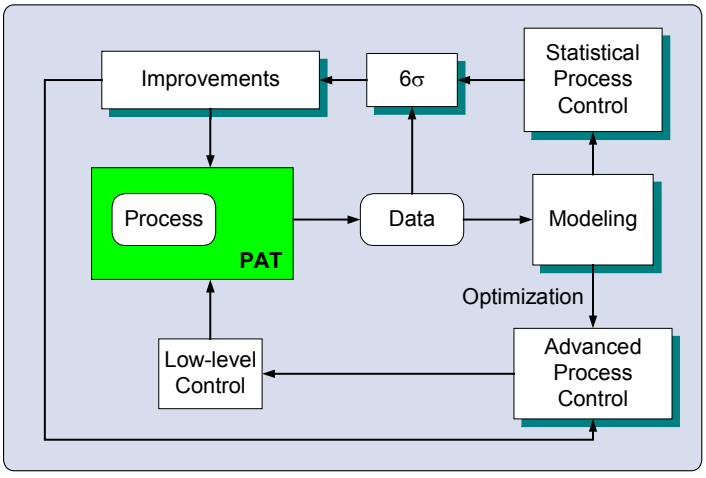

Figure 1 - The role of process systems engineering in biopharmaceuticals manufacture

The five building blocks of the proposed approach allow the investigation of the relationships between process variables and quality and, most important, to affect them. Increasing the sigma-level allows the operating point in the cost–compliance plane to be shifted in such a way that the process compliance is ensured, while at the same time *increasing* the profit margin, as shown in Figure 2. This is an important outcome, since it permits continued compliant production even when subjected to drifts.

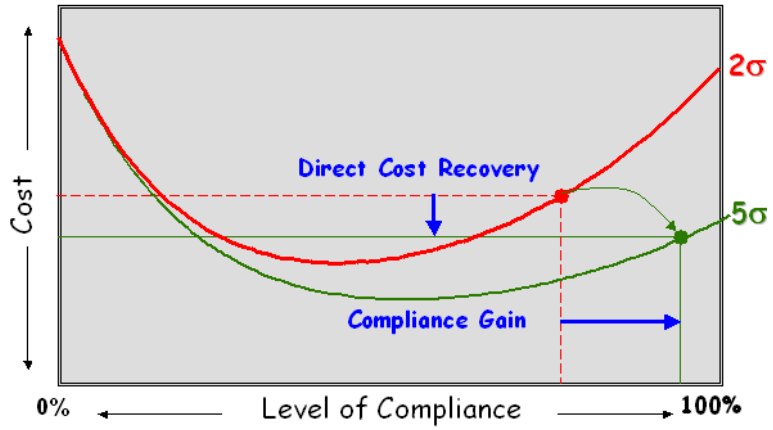

Figure 2 - Cost–compliance plane

In this presentation, our methodology is demonstrated on a case study, involving the analysis of a complete process for the production of penicillin [4], where improved process control and modified substrate-feeding profiles in the fermentor can achieve a 40% reduction in batch time without significant quality losses. The results indicate that our approach can make a substantial impact in the pharmaceutical industry, through improved overall process yield, quality and return on investment.

References

[1] Pharmaceutical Industry: www.csustan.edu/manage/harris/industry1.html.

[2] http://www.phrma.org/

[3] Seider, W. D., J. D. Seader and D. R. Lewin (2004). *Product and Process Design Principles*: *Synthesis, Analysis, and Evaluation*, John Wiley and Sons, New York.

[4] Birol, G., C. Undey and A. Cinar (2002). "A Modular Simulation Package for Fed-batch Fermentation: Penicillin Production," *Computers & Chemical Engineering*, **26**(11): 1553-1565.