A PSE APPROACH FOR YIELD ENHANCEMENT IN BIOPROCESSING

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

Abstract

Improving the sigma level of a pharmaceutical process leads to reduced cycle times, and increased overall efficiency and quality. These objectives can be achieved using an approach involving: (a) *Process Analytical Technologies* (PAT), for data extraction; (b) *Six-sigma methodology* that 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; and (d) *Advanced process control* (APC) and *statistical process control* (SPC). This methodology is demonstrated on a simplified process for the production of penicillin including a fermentor and the first of the downstream processing steps. We show that a combination of improved process control in the downstream processing sections as well as a modified substrate feeding profile in the fermentor, can together achieve a 40% reduction in batch time while at the same time significantly increasing throughput yield. Evidently, this systematic approach can make a substantial impact in the pharmaceutical industry, through improved overall process yield, quality and return on investment.

Keywords

Process Systems Engineering, Bioprocessing, Six-sigma, Yield Enhancement and Downstream Processing.

1. Introduction

Active Pharmaceutical Ingredient (API) production can be divided into two major parts: reaction/fermentation, where the API is produced from the bio-system, and separation/purification, to satisfy product quantity and quality specifications. In the pharmaceutical industry, the purification process is the important one since an unpurified product cannot be marketed. In contrast, however, the overwhelming majority of activity published in the literature has focused on the study of reaction or fermentation, rather than in the downstream processing. It is reasonable to question whether the fine tuning of the fermentation section of the bioprocess is justified, or whether more effort should be invested to improve operations in downstream processing, or better yet, to take a plantwide stance in the design and optimization of the process (Bogle et al., 1996). A plantwide stance calls for a systematic method such as Six-sigma that can serve both as a marker and as the driving force for continuous improvement by identifying the root cause or causes of low process yield, due to excessive variance in the desired performance. As this poor performance could be the outcome of either a poorly design process, or its control system, or a combination of the two, by improving the most significant drawbacks will generally improve the process controllability and resiliency leading to increased sigma levels (Seider et al., 2004). It is important to point out that process understanding is vital in selecting appropriate output variables that can both reflect quality and can be easily controlled. For example, the penicillin extraction yield is strongly affected by the selected operating temperature and pH (Kheirolomoom et al., 1999).

* To whom all correspondence should be addressed. Email: dlewin@tx.technion.ac.il; URL: http://pse.technion.ac.il

2. Proposed Plantwide Improvement Method

In response to these issues, we propose a plantwide approach, combining five main components, as shown in Figure 1, to improve the overall yield in bioprocessing:

Process Analytical Technologies (PAT) an envelope surrounding the process, providing for data extraction, local control and failure diagnosis, and involving instrumentation as simple as a temperature indicator to more complex ones such as NIR or in-line HPLC. The ability of this envelope to perform automated data acquisition and data-transfer in real time is vital to enable process improvements;

Six-sigma methodology (6σ, Rath and Strong 2000) serves as the driving force for continuous improvement by assisting in the identification of the root cause or causes of low process yield;

Process modeling, based on systems biology and first principles models, which provides a basis for model-based control;

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;

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

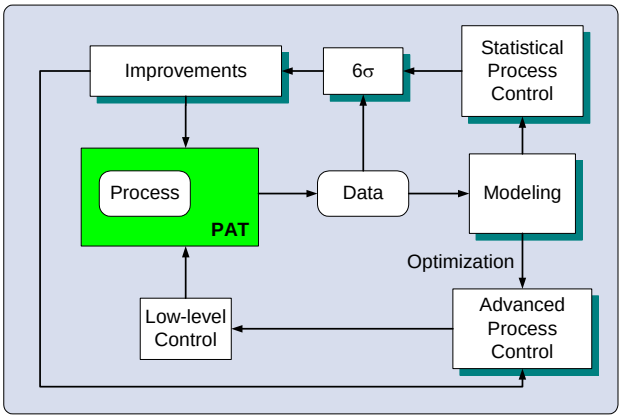

Figure 1. The role of process systems engineering in biopharmaceuticals manufacture.

The five building blocks of the proposed approach allow the investigation of the relationships between process variables and quality and, most importantly, to affect them. As shown in Figure 2, 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. This is an important outcome, since it permits continued compliant production even when subjected to drifts.

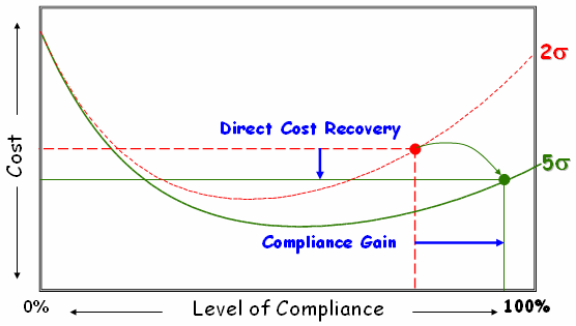

Figure 2. Cost-compliance plane.

In 6σ methodology, an iterative five-step procedure is followed to progressively improve product quality. The five steps are: (a) Define, (b) Measure, (c) Analyze, (d) Improve, and (e) Control, referred to by the acronym, DMAIC:

Define: First, a clear statement is made defining the intended improvement. At this stage, the main focus is on customer concerns, which are used to define critical-to-quality (CTQ) and/or critical-to-productivity (CTP) output variables.

Measure: The CTQ variables are monitored to check their compliance with the UCLs and LCLs. The data for the critical quality variables are analyzed and used to compute the number of defects per million opportunities (DPMO):

$$\mathrm{DPMO} = \tfrac{1}{2}10^{6}\left(1-\int_{LCL}^{UCL} f(x)dx\right) \qquad (1)$$

where $f(x)$ is the probability of the quality being at a value of x, UCL and LCL are is the upper and lower control limits, respectively. As described in Rath and Strong (2000), the sigma level of a process is directly related to its DPMO.

Analyze: When the sigma level is below its target, steps are taken to increase it, starting by defining the most significant causes for the excessive variability. This is assisted by a systematic analysis of the sequence of steps in the manufacturing process, and the interactions between them. Using this analysis, the common root cause of the variance is identified.

Improve: Having identified the common root cause of variance, it is eliminated or attenuated by redesign of the manufacturing process or by employing process control. Seider et al. (2004) present several examples in which process redesign can improve the controllability and resiliency of a process, and hence, reduce the variance in controlled output variables. Alternatively, feedback control can be installed, which transfers product variability to manipulated variables such as a neutralizing stream in pH control.

Control: After implementing steps to reduce the variance in the CTQ/CTP variables, this is evaluated and main-

tained. Thus, the DMAIC procedure is repeated in cycles to continuously improve process quality. Note that achieving *6σ performance* is rarely the goal, and seldom achieved.

3. Demonstrative Example

The proposed methodology is demonstrated on a simplified process for the production of penicillin, considering only the fermentation and the first downstream processing step, as shown in Figure 3. Initially, the DMAIC procedure is applied to define the base-case conditions. Then, cycles of the procedure are implemented to iteratively improve the process.

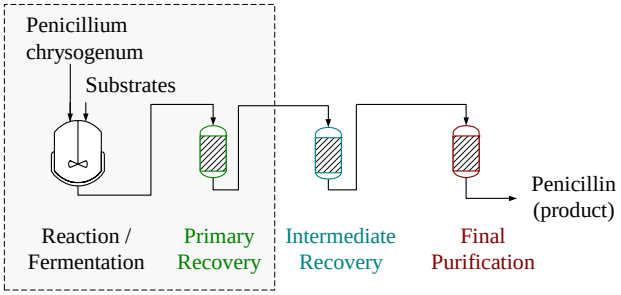

Figure 3. Schematic of simplified penicillin process.

Cycle 1.

Define: For this example, the plant targets were to minimize the overall production time (CTP), to produce a specific concentration of penicillin, while maintaining the CTQ variables, namely pH and temperature, in each unit operation at their setpoints. For this reduced process model, involving only the fermentor and the reactive extractor, the throughput yield, *TY*, is defined as the degree of extraction (in %).

Measure: A detailed model of the process has been developed based on studies from the literature (Bajpai and Reuss, 1980; Reschke and Schugerl, 1984). Next, simulation results are analyzed, and the DPMO calculated using Eq. (1), and presented in Table 1. Note that the overall throughput yield is 79%, which is equivalent to a sigma level of 2.4. Furthermore, operation time for the fermentation to reach a maximum concentration of penicillin was 422 hours and for the extraction operation time was 5 hours.

Analyze: An alternative to adopting a sequential stance and optimizing each unit operation in the direction of flow, the throughput yield can be increased directly by identifying and reducing the most significant causes of variability. Clearly as can be seen from Table 1, the extractor has the highest DPMO and hence it is selected as the prime candidate for improvement. In this regard, additional insight is provided in Figure 4, which shows that the uncontrolled pH drifts and has a negative influence on the degree of extraction that reaches only 79% after five hours of extraction.

Table 1. Summary of control limits, DPMO and TY for the base case.

	LCL	UCL	DPMO	Production Time (hr)
Fermentor				
pH	4.9	5.1	45,445	422
Temperature	22	28	465	
Reactive Extractor				
pH	4.8	5.2	594,485	5
Total Production Time (hr)				427
TY %				79

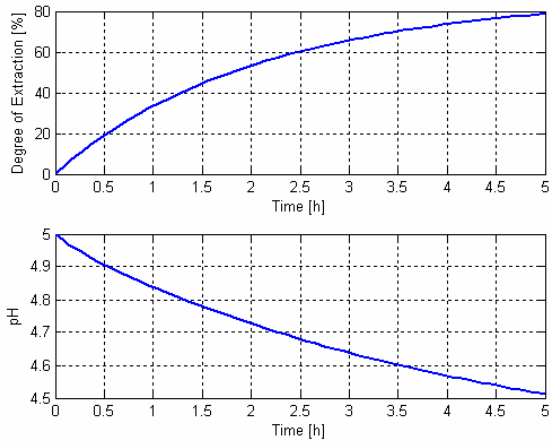

Figure 4. Extractor results – base case

Improve: Having identified the common root cause of variance, it is eliminated by employing process control in the reactive extractor, and as can be seen from Figure 5, also improves the degree of extraction from 79% to 89%.

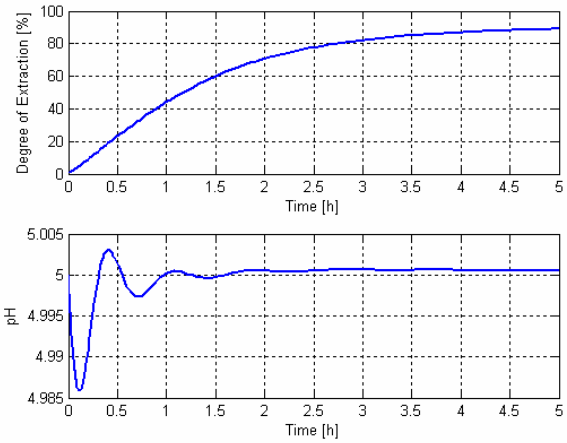

Figure 5. pH control in reactive extractor.

Cycle 2.

Having implemented pH control to improve the extractor operation, the DMAIC procedure is repeated to further improve the process. Drawing our attention to the production time, clearly, the fermentation part takes the largest portion of the overall process time, as shown in Figure 6. A fair question to pose is if it is possible to obtain the same concentration of penicillin in less time. Indeed, this is possible, for example by changing the glucose concentration in the fermentor at which additional substrate is added (i.e., the threshold value) from 0.3 g/l to above 15 g/l. Doing so reduces the fermentation time for a maximum penicillin concentration of 1.5 g/l from 422 to 258 hours, as shown in Figure 7. This reduced production time is achieved at a price of pH and temperature distributions with a higher variance than in the base case, with DPMO levels of 49,628 and 15,625, These DPMO values are higher than the base case, but their increased variance need to be weighed against the resulting reduction in batch time of 40%.

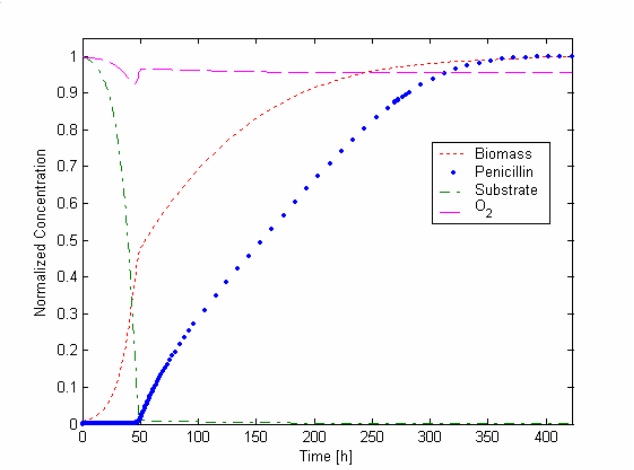

Figure 6. Fermentation trajectories at Cycle 1.

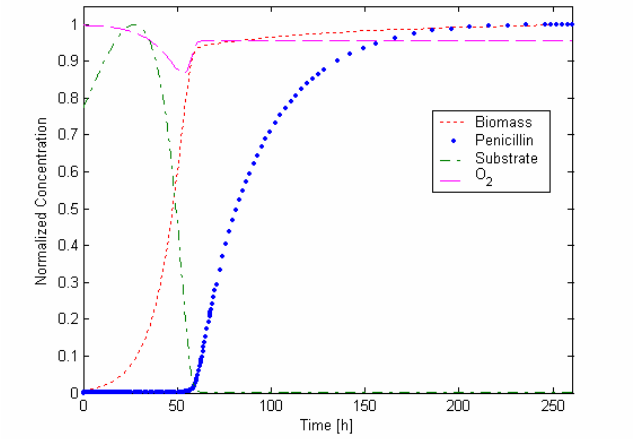

Figure 7. Fermentation trajectories at Cycle 2.

Table 2. Record of improvements using the proposed PSE procedure.

	Base-case	Cycle 1	Cycle 2
Fermentor			
DPMO - pH	45,445	45,445	49,628
DPMO - Temperature	465	465	15,625
Reactive Extractor			
DPMO - pH	594,485	<1	<1
TY %	79	89	89
Production Time (hr)	427	427	263

4. Conclusions

We have shown that our approach, involving a combination of improved process control, modified substrate feeding profiles in the fermentor, as well as improvements in the downstream processing section, can together achieve a 40% reduction in batch time, accompanied by a significant increase in throughput yield, as summarized in Table 2. It has been demonstrated that these improvements arise from adopting a *plantwide* stance in operations, as each improvement has its price tag, budget and time constrains usually limit the total number of improvements that one can perform. Thus, rather than focusing entirely on the upstream process, additional attention is needed in the downstream section(s). Evidently, this systematic approach can make a substantial impact in the pharmaceutical industry, through improved overall process yield, quality and return on investment.

References

Bajpai, R. K. and M. Reuss (1980). "A Mechanistic Model for Penicillin Production." *Journal of ChemicalTechnology and Biotechnology* **30**(6): 332-344.

Bogle, I. D. L., A. R. Cockshott, et al. (1996). "A Process Systems Engineering View of Biochemical Process Operations." *Computers & Chemical Engineering* **20**(6-7): 943-949.

Kheirolomoom, A., A. Kazemi-Vaysari, et al. (1999). "The Combined Effects of pH and Temperature on Penicillin G Decomposition and its Stability Modeling." *Process Biochemistry (Oxford)* **35**(1-2): 205-211.

Rath and Strong (2000). *Six Sigma Pocket Guide*, Rath & Strong Management Consultants, Lexington

Reschke, M. and K. Schugerl (1984). "Reactive Extraction of Penicillin I, II and III." *The Chemical Engineering Journal* **28**(1): B1-B29.

Seider, W. D., J. D. Seader, et al. (2004). *Product and Process Design Principles: Synthesis, Analysis, and Evaluation*, John Wiley and Sons, New York