Chapter 3
The History of OPEX in the Pharmaceutical Industry

Thomas Friedli and Jürgen Werani

The History of Operational Excellence in the Pharmaceutical Industry is still short. Serious initiatives were only launched around 10 years ago. This chapter provides some background on how and why OPEX became a topic of serious interest in this industry.

> As pharmaceutical manufacturing evolves from an art to a science and engineering based activity, application of this enhanced science and engineering knowledge in regulatory decision-making, establishment of specifications, and evaluation of manufacturing processes should improve the efficiency and effectiveness of both manufacturing and regulatory decision-making.[1]
>
> ..., industry's hesitancy to broadly embrace innovation in pharmaceutical manufacturing is undesirable from a public health perspective. Efficient pharmaceutical manufacturing is a critical part of an effective U.S. health care system. The health of our citizens (and animals in their care) depends on the availability of safe, effective, and affordable medicines.[2]

Compared to other industries, the pharmaceutical industry was rather slow to adopt programs to increase Operational Excellence and strive for Continuous Improvement. By the late 1990s, only a few actions with rather limited scope had been taken. In the first decade of the 2000s, OPEX then gained momentum. Since then, OPEX has become a priority not only for the top management and workforce of almost every major pharmaceutical manufacturer, but also for small and

[1] FDA, Final Report "Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach", September 2004.

[2] Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, FDA, September 2004, Page 3.

T. Friedli (✉)
Institute of Technology Management, University of St.Gallen, St.Gallen, Switzerland
e-mail: thomas.friedli@unisg.ch

J. Werani
Schuh & Co, Komplexitätsmanagement AG, Langgasse 13, 9008, St.Gallen, Switzerland
e-mail: juergen.werani@schuh-group.com

T. Friedli et al. (eds.), *Leading Pharmaceutical Operational Excellence*,
DOI 10.1007/978-3-642-35161-7_3, © Springer-Verlag Berlin Heidelberg 2013

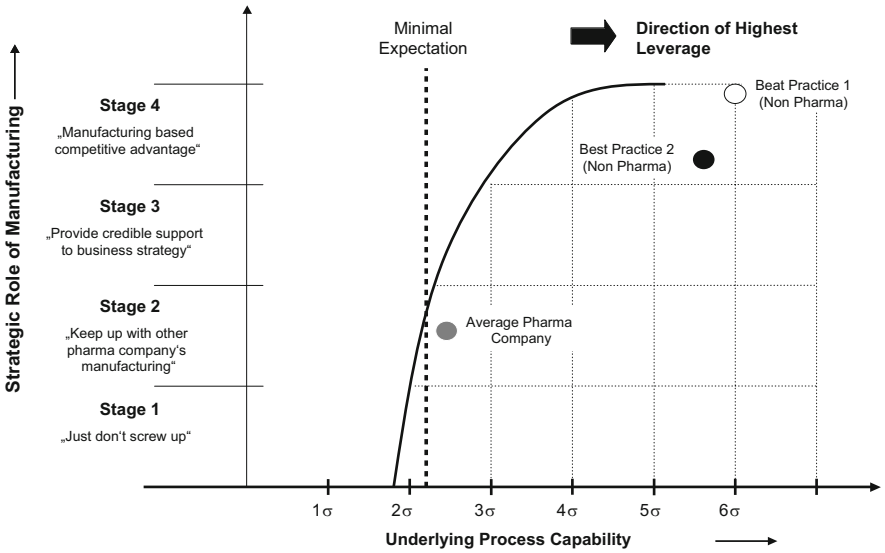

Fig. 3.1 Current status of the pharmaceutical industry (Source: Raju (2003) cited by Kickuth and Friedli 2006)

medium-sized contract manufacturers. Even so, the industry still has a lot to do to catch up with excellence levels of other industries that have been working towards continuous improvement for decades. According to G. K. Raju, in 2003 the sigma level of the pharmaceutical industry was around 2–3 sigma (see Fig. 3.1).

U.S. Food and Drug Administration (FDA) first encouraged serious Operational Excellence efforts in a meeting of the scientific advisory board at the end of 2001. At that time, one of the difficulties the agency faced was the increasing number of post-approval manufacturing amendments (see Fig. 3.2)

This high number of post-approval changes made it difficult for the FDA to fulfill their inspection obligations. It also demonstrated that the industry lacked in the scientific mastering and understanding of its production processes. It was generally agreed that GMP manufacturing worked rather empirically than science-based and that the industry as well as the regulators were risk-averse.[3]

At the same meeting, Doug Dean and Francis Brutton from PricewaterhouseCoopers (PwC) presented a rather bleak analysis of the status quo of pharmaceutical manufacturing. In one of their slides they came to the following conclusions[4]:

- The status quo is untenable
- Pharmaceutical manufacturing – lots of room for improvement
- Traditional metrics hide poor performance
- Compliance infrastructures are not economic

[3] Janet Woodcock (2011).

[4] Bruttin and Dean (2004).

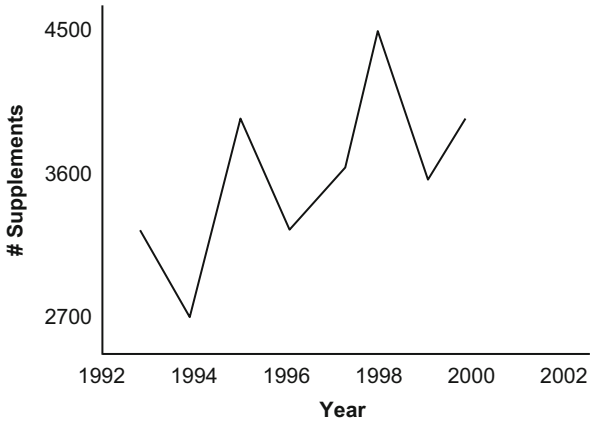

Fig. 3.2 Post approval manufacturing supplements (Woodcock 2011)

- Technologies are critical enablers – but not in isolation
- Huge potential for industry & regulators to create a win-win

They identified some of the reasons for this situation: the transfer of processes that were neither fully understood nor feasible at commercial scales; lengthy and elaborate new product introduction exercises that generated data but failed to provide critical information; 50 % of production costs being locked before the start of Phase III; "institutionalized" process inefficiencies and lacking a scientific basis for the trade-off of investing time and gaining deeper process understanding.

Both the industry and the FDA were well aware of the deficiencies in pharmaceutical manufacturing. To move forward, they jointly encouraged organizations the use of innovative technologies to enhance process understanding and to establish science- and risk-based approaches to quality and regulatory processes. FDA selected Process Analytical Technology (PAT) as a pilot to evaluate how they could further promote the approach of a science-based process management. The PAT team and the manufacturing science work group stated in the executive summary of a report[5]:

> Pharmaceutical manufacturing operations are inefficient and costly. The cost of low efficiency is generally not understood or appreciated (e.g., manufacturing costs far exceed those for research and development operations). Low efficiency is predominantly due to "self-imposed" constraints in the system (e.g., static manufacturing processes, focus on testing as opposed to quality by design, approach to specifications based on discrete or the so called "zero tolerance" criteria, a less than optimal understanding of variability, etc.). These constraints keep the system in a corrective action mode. Continuous improvement is an essential element in a modern quality system and it aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. In the current system continuous improvement is difficult, if not impossible.

[5] Cf. Report of the PAT Team and Manufacturing Science Working Group 2004, Page 1.

In response to these findings, the FDA changed its position: instead of measuring quality by focusing on product purity and potency, more time should be spent on trying to address issues dealing with actual physical manufacturing processes. For example, what effects, if any, do small changes in the reactor vessel, blending, drying, compressing, coating or other manufacturing steps have on the final dosage form?[6] The main objective was to gain a more thorough understanding of pharmaceutical manufacturing processes and thereby more predictable and efficient manufacturing. Although process analytics are potentially the vital tools, the PAT initiative is essentially about process understanding, predictability and efficiency. PAT should be thought of as a system for designing and controlling manufacturing through timely measurements of critical quality and performance attributes, and of raw and in-process materials and processes, with the goal of ensuring superior product quality. Associated with the greater understanding of processes, additional benefits can be achieved, such as faster development of new products; shorter manufacturing cycle times; higher yields; reduced waste materials; and fewer product recalls.[7] The PAT initiative preceded the broader cGMP initiative by about a year. In August 2002, the Food and Drug Administration announced this significant new initiative to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. The main objectives of this initiative were: *(1) to encourage the early adoption of new technological advances by the pharmaceutical industry, (2) to base regulatory review and inspection policies on state-of-the-art pharmaceutical science, (3) to facilitate industry application of modern quality management systems*, *(4) to use risk-based approaches that focus both industry and agency attention on critical areas*; and *(5) to incorporate enhanced quality system approaches into the agency's business processes*.[8]

The initiative also stated a so-called desired state for pharmaceutical manufacturing:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact performance
- Continuous improvement approaches, with innovative use of new technology as desired
- Continuous "real time" assurance of quality

The PAT activities became part of cGMP. Importantly, cGMP was impacted by economic considerations, leading to a new paradigm: Quality and Productivity came on the agency's agenda, opening new opportunities to the industry.

[6] Cf. Clark (2004): FDA's PAT initiative, in: Pharmaceutical Technology Europe.

[7] Clark (2004).

[8] Cf. Report of the PAT Team and Manufacturing Science Working Group 2004.

> Quality and productivity improvement share a common element – reduction in variability through process understanding (e.g., application of knowledge throughout the product lifecycle). Reducing variability provides a win-win opportunity from both public health and industry perspectives. And, since manufacturing technologies and practices are generally similar between both innovator and generic companies, facilitating efficiency improvements provide opportunities for both sectors of the pharmaceutical industry.[9]

With this, Lean Thinking (Operational Excellence) became part of the game.

Later FDA activities were all based on the same underlying idea: to modernize the scientific base of pharmaceutical manufacturing and pharmaceutical quality management. This can be observed in the documents about the "Critical Path Initiative" as well as in the work along of ICH Q8–Q10, in the more recent QbD initiative and the new process validation guideline released in 2011. The regulatory basics will be discussed more detailed later in Chapter 5. Though the idea of "continuous improvement" has become more widespread in manufacturing, adjusting to a new paradigm and overcoming decades of a "no change culture" continues to be difficult and takes both time and effort:

> Continuous improvement is an essential element in a modern quality system. Its aim is to improve efficiency by optimizing a process and eliminating wasted efforts in production. Improvement efforts are carried out in a structured manner with appropriate predefined protocol and oversight. These efforts are primarily directed towards reducing variability in a process and product quality characteristics and are not for changing the fundamental design of a manufacturing process. Generally the term continuous improvement is broadly used for all improvement efforts including those that result from corrective actions. In the regulatory setting a distinction between corrective action and continuous improvement is essential. Need for corrective actions occur when product quality characteristics are in question (e.g., out of specification). Such a situation can require urgent risk assessment and sound quality decisions to prevent any adverse impact on patients. In the current state corrective actions are the dominant mode for improvement and continuous improvement is difficult.[10]

The Critical Path Initiative from 2003 had its own industrialization perspective (cf. Figs. 3.3 and 3.4) and QbD was the logical next step: making sure that introduced processes were better understood from the launch.

In summary, the industry aspirations to reduce (production) costs rooted in the increasingly difficult environment the industry faced. The end of formerly successful business models, increased competition and cost pressure from health care organizations, combined with support from the regulatory agencies opened the way to a new thinking. Operational Excellence became not only an urgent and demanding economic necessity but also was expected to be welcomed by the FDA.

The introduction happened in three major stages described in more detail in Gronauer et al. (2010) (Fig. 3.5).

The first phase was the "pre-OPEX" phase, which lasted until the late 1990s, followed by a "Best-Practice Transfer" phase, which gave way to today's "Transformation" phase. Looking ahead, we have added a fourth phase, an "Integrated

[9] FDA 2004b.

[10] FDA 2004b.

Dimension	Definition	Examples of Activities
Assessing Safety	Show that product is adequately safe for each stage of development	• Preclinical: show that product is safe enough for early human testing Eliminate products with safety problems early • Clinical: show that product is safe enough for commercial distribution
Demonstrating Medical Utility	Show that the product benefits people	• Preclinical: Select appropriate design (devices) or candidate (drugs) with high probability of effectiveness • Clinical: Show effectiveness in people
Industrialization	Go from lab concept or prototype to a manufacturable product	• Design a high-quality product - Physical design - Characterization - Specifications • Develop mass production capacity - Manufacturing scale-up - Quality control

Fig. 3.3 The three dimensions of the critical path FDA (2004a)

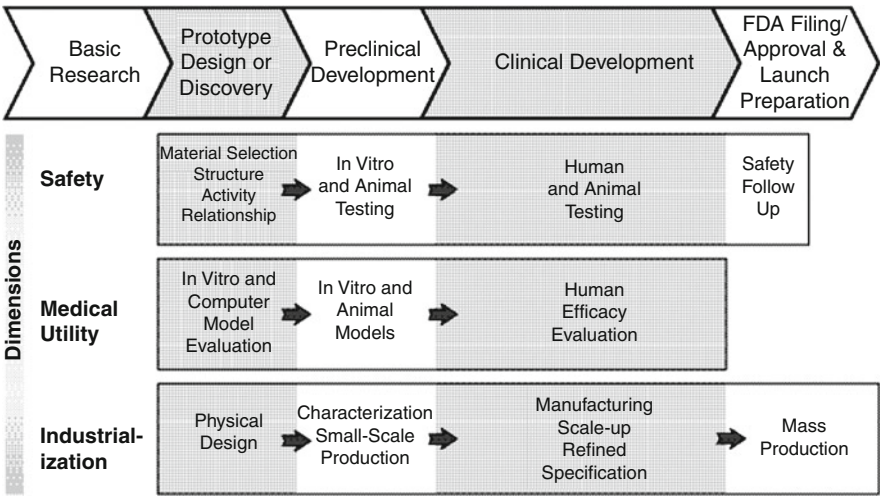

Fig. 3.4 The industrialization perspective along the product lifecycle FDA (2004a)

Operations Systems" phase, which we expect to be the future dominating pattern in the industry. In our opinion, some of today's pharmaceutical companies are already on the threshold of entering this fourth phase. The pathway to OPEX in the pharmaceutical industry and its four phases are illustrated in Fig. 3.5.

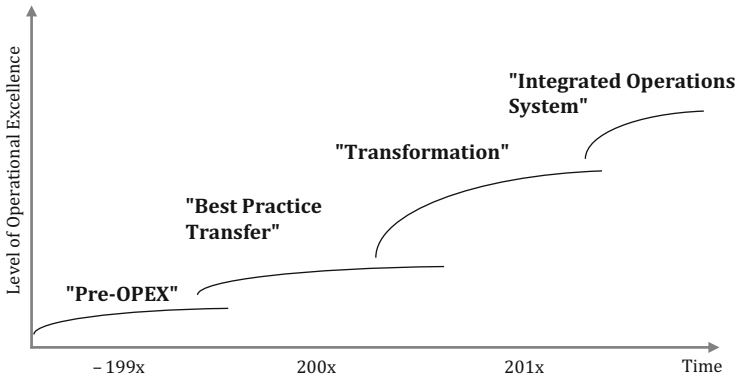

Fig. 3.5 The pathway to operational excellence (Gronauer et al. 2010)

Even today's most advanced OPEX programs, i.e. the ones on the threshold to the "Integrated Operations Systems" phase, have not evolved over night. They, too, went through all the other phases.

The pre-OPEX phase is characterized by isolated manufacturing improvements that were not the result of a structured and carefully designed approach. Changes were only introduced reluctantly; the underlying culture was one of "no-change". The rising cost pressure and new FDA directions (as outlined above) made a new approach necessary. Pharmaceutical production managers visited plants from BMW, Audi, Toyota etc. The main intention was to copy successful lean thinking practices and apply them to the pharmaceutical production floor. After some initial successes, however, it became clear that simply copying methods and tools and transferring training programs did not suffices to get a buy-in from employees.

The next phase therefore focused on people, and was designed as a huge change management approach. Most of the more advanced companies still are at this transformation stage. We foresee, however, more integrated approaches in the near future that will, on the one hand, bring together preventive and reactive OPEX (e.g., QbD and OPEX combined) and, on the other hand, align all improvement initiatives on the top management level. This is a necessity to ensure employees understand the great potential and benefits that OPEX offers a company.

Conclusions

A combination of reasons led to the rise of OPEX in the industry: The increased pressure on drug prices, the often cited productivity crisis in pharmaceutical R&D, but also regulatory agencies' increased focus on bringing science to pharmaceutical manufacturing processes. The industry has overcome initial beliefs that success could be achieved by copying training plans, methods and tools from other

industries, and has adapted new, unique approaches dealing with people in the organization. Most of the examples in parts II and III of this book evidence these developments.

References

Bruttin F, Dean D (2004) Managing the cost of compliance in pharmaceutical operations. http://www.efcg.cefic.org/fdxdownload_13.iK23abe1ee02e8be1e/publication_file/managing-the-cost-of-compliance-in-pharmaceutical-operations.pdf. Retrieved 22 January 2013

Clark G (2004) FDA's PAT initiative, in: pharmaceutical technology Europe. http://www.pharmtech.com/pharmtech/Analytical/article/detail/129539. Retrieved 20 January 2013

FDA (2004a) Challenge and opportunity on the critical path to new medical products. www.fda.gov. Retrieved January 2010

FDA (2004b) Final report "pharmaceutical CGMPs for the 21st century – a risk-based approach", September 2004. www.fda.gov. Retrieved January 2010

Gronauer T, Friedli T, Götzfried M (2010) The roadmap to operational excellence – pattern and elements of OPEX programs. In: Friedli et al. (2010) The pathway to operational excellence – overcoming the internal inertia. Editio Cantor Verlag, Aulendorf

Kickuth M, Friedli T (2006) The pharmaceutical plant of the future. In: Friedli T, Kickuth M, Stieneker F, Thaler P, Werani J (eds) Operational excellence in the pharmaceutical industry. ECV – Ed.-Cantor-Verl, Aulendorf

Report of the PAT Team and Manufacturing Science Working Group (2004) Innovation and continuous improvement in pharmaceutical manufacturing – pharmaceutical CGMPs for the 21st century. www.fda.gov. Retrieved January 2010

Woodcock J (2011) Presentation, meeting of the FDA science board, November 16th, FDA, Regulation of drug quality: new challenges. www.fda.gov. Retrieved 20 January 2013