The Pathway to Operational Excellence

in the Pharmaceutical Industry

Overcoming the internal inertia

Edited by
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Prabir K. Basu
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Juergen Werani

EDITIO CANTOR VERLAG

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Foreword

We are pleased to introduce this book, which explores the recent trends by leading pharmaceutical companies to implement Operations Excellence (OPEX) practices and the unique challenges they are facing. The industry has been slow to adopt such practices, which have been commonplace in sectors such as electronics, high tech and automotive for over twenty years. The reason for this has been the relative success, in the past, of the pharma industry, which did not create a compelling need for manufacturing and supply chain operations to be as efficient as they could.

In addition, many pharma organizations display an inertia which is a powerful factor to face for pharmaceutical operations, inside and outside a company.

Inside: the word "quality" must be redefined and thought not only as a way to meet regulations but also to produce in shorter cycle time, with less transport, waiting, inventory, work in process, waste and energy. In one word, to produce more efficiently. Where in the past, quality was "inspected in" after the fact, the future will see more "design for manufacturing" and "quality at source" considerations. There is a strong resistance to change within the industry and the attitude of "we have always done it this way" works against the idea of continuous improvement. Overcoming this attitude is the most challenging part of this "journey".

Outside: Authorities recently started collaborating to improve innovation. In its "Pharmaceutical cGMP for the 21st century" white paper, FDA stated that "as pharmaceutical manufacturing evolves from an art to a science and engineering based activity, application….should improve the efficiency and effectiveness of both manufacturing and regulatory decision-making".

However, there remains a lot of work to be done.

In this challenging phase for pharmaceutical operations, it is important to close the gap with the other industry sectors, which have already implemented tools and methodologies to improve their performance and efficiency. We are just beginning to adopt Best Practices from other industries. But a key question is whether these Best Practices can translate across to pharma. Many can likely be directly adopted and some may need to be adapted for the "pharma environment".

For instance, when we talk about "lean manufacturing", the question is how can you apply a strategy that has its roots in the car industry?

A common feature of the lean philosophy is to reduce the production batch size. In pharma, the batch size is normally fixed when the product is registered with the regulatory agencies and cannot easily be changed.

That is often enough for some companies, to say that Lean doesn't work for the pharmaceutical industry. But even the concept of "batch" should be renewed. Some big pharma companies are studying with equipment vendors new systems to make solid continuous manufacturing, using Process Analytical Technology (PAT) and smaller equipment. The results could be a batch size defined no more as a physical volume but as time unit, especially for continuous processing systems.

And even if it's not possible to convert a process, pharma plants can be otherwise reorganized to create a continuous flow, putting together and creating the sequence of different process steps, with minimum material movements between them. We are used to seeing manufacturing plants organized by technological departments, such as: dispensing, granulation, tabletting, coating, blistering and packaging, quality control labs.

Each of them works independently and follows its own scheduling, with little or no consideration of the actual needs of next step. This means that between each stage and the next one, you will find a huge amount of intermediate materials as "work in process" (WIP): pallets moving through the plant and then stored, waiting to be processed or analyzed.

Nobody has the full visibility and control of the product's flow. Future plants should be quite different: cellular flow layout, pull systems instead of push, no intermediate product store, quality control within the manufacturing area, line supervisors instead of department supervisors. One only "big goal" for everybody working together on the shop floor: to get the product out of the plant. In traditional plant layout, people have different goals: to push out the materials from their department to the next one.

In conclusion, this book chronicles the start of an important journey which still has a long way to go but, at least, the journey has started!

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Foreword

The jointly published benchmark study, "Operational Excellence in the Pharmaceutical Industry" by the APV (International Association for Pharmaceutical Technology, Mainz, Germany) and the TECTEM (Transfer Center for Technology Management, University of St. Gallen, Switzerland) in 2006 led to an industry-wide rethinking and reevaluation of pharmaceutical production. However, this was only the beginning of a long lasting process which had to overcome many difficulties especially in implementation. The study helped pharmaceutical companies understand the need to scrutinize production as well as the corresponding supporting processes.

The steady changes in the basic conditions for the pharmaceutical industry, e.g. the build-up of low-cost production capacities outside Europe and the US, changed reimbursement schemes in the public health system in many countries, a changing product portfolio, decreasing batch sizes, the introduction of Process Analytical Technology (PAT) as well as Quality by Design (QbD), and the trend towards individualized medicine further pushes the evolution of these production systems. The pharmaceutical industry cannot and should not ignore these changes. It has to face them as other industries have done 20 years ago or more and has to reinvent itself.

One of the biggest challenges is definitely dealing with the people who implement and develop a production system against the background of Operational Excellence (OPEX). This is where most mistakes are made, which sometimes results in the loss of employees whose knowledge is desperately needed in the processes.

This book discusses these and additional challenges and presents many case studies. Compared to the 2006 edition, it has gone a big step further in the direction of reviews on the implementation, practicality and consequences of OPEX for the production system. One of the strengths of this book is the variety of authors and contributing companies and therefore the collection of different point of views. It is in the nature of things that no universal solution is offered. Rather, the book provides a broad view on different but integrated concepts, tools, and examples. This helps to set the stage for companies who are on the way to OPEX and helps them to select the specific instruments needed for their individual path.

This second edition is going to be as successful as the predecessor. This is an easy prediction to make as the time for a broad implementation of OPEX in the pharmaceutical industry is urgent and important.

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Managing Director

APV (International Association for Pharmaceutical Technology)

Mainz, Germany

Section A

Introduction

The Pathway to Operational Excellence in the Pharmaceutical Industry – Overcoming the Internal Inertia

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Leading pharmaceutical companies all over the world are facing a "new reality". Whereas, in the past, value creation was mainly based on intellectual property and market exclusivity, the blockbuster business model was the major source of cash flow for most of these companies. Today's "new reality" is characterized by shrinking R&D productivity, cost-reduction initiatives from payer organizations – mostly driven by governmental pressure, shifting global growth, increased regulatory requirements and loss of market exclusivity for many of the late 20th century blockbuster drugs. Despite this steadily increasing pressure we are still optimistic for the industry as a whole; however, new solutions to fundamental strategic issues must be found. This is especially important when dealing with the role of manufacturing and supply organizations and the way these organizations are managed and administrated. Pharma companies have now entered an era that other industries reached decades ago and, based on these developments, Operational Excellence (OPEX) in pharmaceutical manufacturing must take its place as the cornerstone of every sustainable operations strategy in this industry.

While in the past the pursuit of product and substance innovations was the key issue in the pharmaceutical sector, the manufacturing process remained mostly static. Those times are gone and now, both the need for and the speed and scope of continuous improvement within manufacturing will steadily increase in the future. The key to excellence in this area is a focus on people. They design, operate, improve and re-invent activities, processes, systems and structures and we believe that it will be the ability to make each individual employee think in terms of change that will overcome the organization's internal inertia and separate the winners from the losers.

I.1 The Structure of the Book

How to structure a book? For every publisher and editor this is one of the most challenging questions! From our perspective, the pathway to OPEX in pharma today is really a journey into

new terrain for the whole industry. One of the important lessons learned over the last number of years has been that the path is not as clear as it had been expected and that you cannot explore this new terrain alone. Indeed, standardized implementation roadmaps from external consultants, one-size-fits-all solutions and so-called 'experts' acting like mavericks have been quite unsuccessful. The challenges of OPEX, as we see them, are characterized by uncertainty, a need for true teamwork, and for technical as well as behavioral leadership skills.

A more in-depth look brought us to the conclusion that this journey has much in common with the expeditions in the 18th century, when courageous sailors explored more of the uncharted territories of our world. Often under a cloud of uncertainty, the captains could not accomplish these feats alone; they had to rely on their crews, ships, and emerging navigation techniques. Today's OPEX champions face a similar situation; therefore, for inspiration we looked at one of the journeys of Captain James Cook.

When James Cook left Plymouth harbor (Great Britain) aboard the HMS Endeavour (a modified three-masted sailing ship with a length of 30 meters and a width of only 9 meters!) on August 26, 1768, he was taking responsibility for a crew of 98 men as they sailed to face an uncertain destiny. Their journey took almost three years, during which time Cook's crew of 75 seamen, 12 soldiers and 11 scientists, illustrators and service people was away from their homes and their families. The combined mission given to him by the Royal Society and British Admiralty required Cook to lead his men in adverse conditions. First he was to sail to Tahiti to observe and to record the transit of the Venus as part of a scientific experiment and later he was to find and conquer the mythical and unknown continent „Terra Australis Incognita" for the British Empire. However, it was not only his courage in the face of uncertainty and his natural leadership skills that allowed Cook to succeed; he also possessed special technical skills. These skills would later revolutionize the navy in general and turn him into one of the most famous figures of his century.

With the hiring of James Cook as commander of a royal mission, the admiralty had made a rather atypical decision. James Cook was born in 1728, son of a day laborer in North England. He started working on a coal freighter as a 'ship's boy' when he was 17 and joined the Royal Navy in 1755. Obviously he was not one of the aristocratic officers that had been so typical in the Royal British Navy at that time; instead he was a talented man with experience and a convincing track record.

After entering the Royal Navy he became interested in the art of military cartography and the process of navigation by a plane table, spacer, and goniometer, which fascinated him. During the Seven Years' War he mapped the entrance to the Saint Lawrence River and facilitated the famous Royal Navy attack on the Plains of Abraham, a key moment for the British Empire and a deciding moment for Cook, as it demonstrated his skills to the admiralty.

Cook became more and more fascinated by the various methods of mapping and cartography, but he saw how dilettante most navigators and captains were with regard to these methods. He started to learn more about mathematics, astronomy, and navigation to perfect these techniques. By continuously improving his approach, he differentiated himself from other captains, who navigated mostly along visible coastlines, or by often inaccurate observations of the stars. Through his endeavors Cook became a master in navigation techniques and a strong leader.

His combination of seamanship, superior surveying and cartographic skills forged him into an outstanding man who ultimately received the rank of a Captain in the Royal British Navy. He sailed into the unknown South Seas three times, navigated his ships through dangerous waters, even crossing the dangerous Great Barrier Reef with his, by comparison to other vessels, tiny, wooden ship and he was the first man to sail the Antarctic Circle. Sometimes he seemed to be obsessed with exploring dangerous locations in order to confirm or refute commonly

accepted "facts" but Cook was also well known for the fact that his ships had seldom been in great danger and the mortality rate of his crews was one of the lowest amongst all Royal missions. One reason for this were Cook's activities relating to scurvy. More than other commanders before, he investigated this disease and took great care with diet plans for his crew. Following his second journey James Cook was announced as a member of the Royal Society in recognition of his studies of scurvy.

In many ways, James Cook and his journey are an excellent reference point for what operations leaders in pharma are facing today. On one hand, the pharma world is changing faster than in the past, market structures are shifting, unknown terrain and market segments are emerging and courageous changes may be required. On the other hand, new paradigms of operational techniques and methods are going to revolutionize a system which, while good for the „older times", will not be a suitable fit for the „new reality" that we face. We have chosen a „journey report" as an analogy. To our understanding it reflects quite well on the often neglected points of uncertainty and sustainability. As with real expeditions, people first need to know the starting position, before defining the destination, setting the direction, gaining awareness of the terrain that they will face and looking for good maps, team members and equipment.

Therefore we have divided our journey report into four parts.

I.2 Starting Point of Our Journey

Before you define the destination and consider the best route to get there, an essential part of navigation is to identify your starting position. Whether you will finally reach your chosen destination, and achieve your long-term goals depends on how you are equipped for this journey, on your skills and capabilities. Let us look at the example set by Cook. His first destination was Tahiti, a tiny island in the Pacific Ocean. As previously mentioned, the common navigation approaches at the time were „following the coastline" or making a rough calculation based on the position of the stars. With these approaches it would have been pure luck to find Tahiti. Consequently, Cook perceived that improved navigation skills were a key skillset for the mission's success.

Therefore our book begins with an overview of the actual state of the pharmaceutical sector today, the level of operational performance and the biggest gaps. We continue by considering which „methods and tools" are available to us in our goal of achieving OPEX and what the status of their actual implementation is.

Gronauer and Friedli (University of St. Gallen) start by analyzing which trends, in (I) global customer demand and healthcare systems, (II) product innovations and product portfolios, (III) value chain, capacities, sourcing and cooperation, (IV) process innovations and technologies, and (V) the regulatory framework, may have significant impact on manufacturing and supply strategies. In summary, the industry's main challenges are loss of market exclusivity, an increasing number of failing product candidates, unsecure product pipelines, uncertain assumptions about future volumes and market growth outside of mature markets, and the success of new cost-competitive players. Manufacturing will need to become more complex and agile to handle uncertainty, but it is not supportable to achieve this by paying the "price" of higher costs. To overcome this trade-off, existing paradigms have to be questioned.

Herlant (The Boston Consulting Group) discusses these challenges by focusing on the link between manufacturing strategy and business strategy. Indeed, for many pharmaceutical

companies in which product differentiation is fading away, a breakthrough improvement of performance is required to achieve cost leadership and remain prosperous in the "new reality". The case of cost competitiveness, the new demands on operations concerning flexibility and agility, the value of a consistent framework for manufacturing network strategy, the rebalancing of risk-pooling and internal control, and adjustments in supply strategies are some of those strategic manufacturing issues which may be key for outperforming operational capabilities in the future.

Basu (National Institute for Pharmaceutical Technology and Education, NIPTE/Purdue University) takes a closer look at today's operational efficiency and the scientific understanding of pharmaceutical manufacturing as well as the major changes in the regulatory environment. Basu's status report and call for changing from Quality by Inspection to Quality by Design is one of the most crucial and also challenging issues for the future. The agencies have outlined their views on the future of pharmaceutical manufacturing. Nevertheless, the path to this future is still blurred and orientation for companies that are starting their journey is needed.

Duennebier *et al.* (Bayer Technology Services) describe how the change process in pharmaceutical production can be initiated by means of modern technologies, analyzing tools, advanced information and control systems, implemented under the banner of Process Analytical Technologies (PAT). The spread of comprehensive automated process control systems has been slow in the past but is now increasing significantly. However, the largest savings will be addressed by integrating all relevant parts of the supply chain and the design of „more robust processes".

Goetzfried *et al.* (University of St. Gallen) present an additional analysis of the performance and implementation level of major OPEX practices such as Total Productive Maintenance, Total Quality Management, Just-In-Time strategies and an Effective Management System. Their analysis is based on insights from the largest independent OPEX survey for pharmaceutical manufacturing and quantifies the development from the first survey in 2004 up to the current time. They reveal that pharmaceutical companies took control of their former low asset utilization and managed to improve the efficiency of their quality systems, but are still far away from having any kind of „continuous flow", smooth production scheduling or make-to-order manufacturing.

Together, these different status reports provide a detailed view of the current OPEX implementation and an outlook for the future.

I.3 Maps and Experiences

As previously mentioned, James Cook had superior surveying and cartographic skills. His maps were among the best in the world, indeed, some of them were still in use at the beginning of the 20th century.

This part of the book focuses on creating and using the right maps, i. e. a map that helps the explorer to make a decision about the best possible route to reach his destination. Practical experiences from leading pharmaceutical companies support these reflections on the most appropriate route for a specific company on its journey to OPEX, i. e. which steps are required and which elements should be combined. We begin with the insight report on Pfizer's way to OPEX by Migliaccio *et al.*, one of the most cited initiatives which had already been started

back in 2003. After this we focus, together with Crossman, on the experiences Wyeth made in transforming the culture of the organization towards continuous improvement. We explore the approaches from Roche and Genentech described by Griffith *et al.*, and also take a look at the future combination of these two into one single integrated approach for Roche/Genentech. Along with the Merck Serono example, described by Caloz and Wedemeyer, we will give insights into an approach to better foster knowledge management within a global production network. We close this part of the book with the Novartis approach to OPEX by Dreamer, relying heavily on process orientation and flatter hierarchies.

As a conclusion to this section Gronauer *et al.* outline a phase model for the development of OPEX that aims to better understand the underlying logic of the different initiatives in place all over the world.

I.4 Exploring the Landscape

When James Cook left Tahiti, a young Polynesian man called Tupaia who had explored many of the French Polynesian islands, joined the crew. Tupaia's remarkable navigational skills and especially his local Pacific geographical knowledge proved invaluable for Cook's onward journey, especially for navigating the Polynesian islands and later in negotiations with New Zealand's Maoris.

Now that we have learned more about the different maps and gained eye-opening experiences, we need to explore the unknown territories. In a similar fashion to Cook we look for first hand information and personal experiences. In this part of the book, we visit the hot spots that have been discovered and seek out insider tips. Having framed our journey in the previous section, we now have to gain valuable insights and first hand experiences from the terrain we will have to cross.

Friedli *et al.* introduce a model which helps to understand and assess eight key influencing factors for a sustainable OPEX implementation on site level. They give an overview of the critical factors that either support or hamper the sustainable implementation of OPEX, a tool for analyzing improvement potential at site level, and for the identification of useful knowledge exchange opportunities within a network. Finally they provide helpful recommendations on corporate commitment, organizational inertia, site culture and management commitment, organizational structure, engaged staff, implementation processes and integration approaches. In addition, valuable insights into the terrain of OPEX training are given in the article from Werani *et al.* (Schuh & Co. Complexity Management) discussing the creation of a training organization and the scope of the primary content.

In addition we receive helpful reports on selected powerful tools. For the strategic and tactical level, the Operational Scorecard introduced by Docherty (i-nexus) provides an approach for tracking improvements, steering at management level and guiding implementation that is required for aligning the activities.

For the operational level of our journey, two fundamental tools, namely "Value Stream Mapping" and Six Sigma analysis, are presented by Werani *et al.*, showing the entire implementation process and possible business impact in a comprehensive manner. Riehle (Bayer Technology Services) highlights the communicative aspects of OPEX and its „interconnection" between different organizational layers as well as between technical systems and operators. He also discusses a three level framework for linking field operations with operations and corporate management by integrating process technology and process management.

Last but not least, we examine the use of brand-new technologies and process innovations. Weyhers and Bernhard (Pfizer) give valuable insights into NEWCON, which was awarded „Facility of the Year" in 2008 by the ISPE in the category of "Process Innovation". Bisson *et al.* (Novartis) take a broader look at the horizon of technology and continuous flow; the blue sky vision from the Novartis-MIT Center for Continuous Manufacturing describes a visionary path for the industry.

I.5 Redefining the Destination

In the 18th century, a large portion of the globe was unknown to the European nations. There was no reliable cartographical data on these unknown areas, and very few „maps" covering these unknown territories were available. The approach in use was called „speculative cartography". While in some cases having these maps had been better than having nothing at all, it was important to know and understand that these maps were only based on speculations and that they had to be reshaped by authentic experiences and discoveries.

Since the Geographole Hyphegesis by Ptolemy (100 AD – 175 A) Europeans believed that a huge continent existed on the south side of the world. People believed that the Indian Ocean was enclosed by land to the south and that the lands of the northern hemisphere should be balanced by land in the southern hemisphere. They called this mysterious landmass „Terra Australis Incognita". Even though nobody had proven its existence, the belief in „Terra Australis Incognita" was quite strong and as a result James Cook received instructions to explore this unknown continent. New Zealand, first seen by the Dutch explorer Abel Tasman in 1642, was regarded by some as part of this continent. It is one of history's ironies that Cook became the person who proved that this huge land mass did not exist, meaning that leading European scientists of the time had to reshape their picture of the world and their knowledge of it.

While the scope of the known world was expanded from the northern hemisphere to the southern, the scope of OPEX has gone from a pure internal manufacturing issue to a company-wide understanding. As we have seen, the most successful OPEX programs reshaped their understanding and scope at deciding moments and redefined their destination.

Within the last chapter we will summarize the development of OPEX today and point out the biggest challenge that lies ahead: the integration and alignment of different programs and initiatives. Basu shows how Quality by Design (QbD) and OPEX reinforce one another, that QbD starts with the specifications of the product and that OPEX should move on to superior product design. Finally, Friedli and Gronauer consider today's challenges to integrate different improvement programs and partners into existing OPEX approaches.

II In Retrospect: A Summary of Operational Excellence in the Pharmaceutical Industry in 2006

Thomas Friedli and Matthias Goetzfried

University of St. Gallen (Switzerland)

II.1 Our Operational Excellence Reference Model

Our Operational Excellence (OPEX) reference model was created by adapting integrated production models already existent in other industries to the specific needs of the pharmaceutical industry. Treating OPEX as an integrated system, it served as a "thought model" for the questionnaire in the benchmarking study. The original model from 2006 is shown in Figure 1.

Our OPEX reference model includes several sub-systems. Each sub-system represents in itself an important part which contributes to the overall success. In fact, the included elements reinforce each other. According to this model, manufacturing is viewed as a system in which single elements or interventions have a direct and indirect impact on other elements or sub-systems. For example, a deeper implementation of process management has to be seen in close linkage with practices such as clear target setting, visible leadership commitment and visual management.

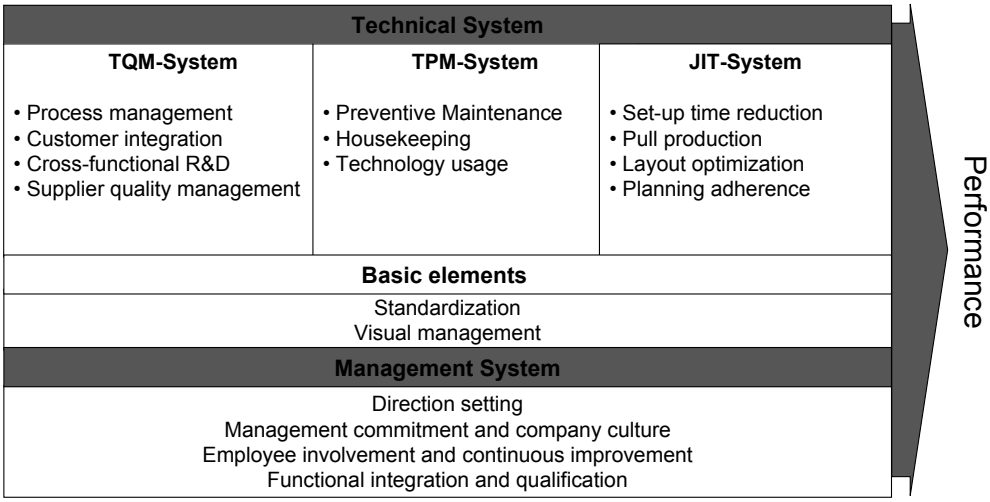

Figure 1: OPEX reference model from 2006.