I 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

V Operational Excellence Benchmarking – Quantifying the Advancements from 2004 to 2009

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Many pharmaceutical companies claim to have achieved a remarkable level of Operational Excellence (OPEX) similar to that of established "lean enterprises" in other industries. The term "Operational Excellence" has spread throughout the entire industry since several years. Companies are celebrating their successes in OPEX initiatives, telling impressive stories e. g. of 80 % lead time reductions. Some companies even describe their own transformation, for which Toyota needed decades, as „already finished".

However, a broader look into the industry taken by the research project „Pharma OPEX Benchmarking"[1] at the University of St.Gallen may be disillusioning. Based on the model presented by Friedli and Goetzfried[2] the project shows a different reality across pharmaceutical companies. By pointing out the advancements and setbacks of the industry from 2004 to 2009, this part of the book draws a balance from half a decade "Operational Excellence in the Pharmaceutical Industry".

In the following paragraphs the changes during five years (2004 until 2009) are described in detail and substantiated by numbers of the ongoing research project "Pharma OPEX Benchmarking". A comparison of the 2004 and 2009 results is presented with the focus on the four sub-systems: Total Productive Maintenance, Total Quality Management, Just-in-Time, and the Effective Management System. Key performance indicators ("metrics for tracking progress and comparing with other companies") and enablers ("methods and tools leading to top performance") are analyzed and interpreted for each of the categories. To give a comprehensive interpretation of the industry's development, the following analysis uses the median scores surveyed by the benchmarking for each sub-system[3].

V.1 Total Productive Maintenance

Did Pharmaceutical Companies Establish an Efficient Management of Fixed Assets?

A boost in Overall Equipment Effectiveness (OEE) combined with an increase of unscheduled maintenance due to direct stoppages show the inconsistency in Total Productive Maintenance

[1] See *http://www.opexbenchmarking.com*

[2] See Friedli and Goetzfried, In Retrospect: A Summary of Operational Excellence in the Pharmaceutical Industry in 2006, Figure 7 (p. 33).

[3] See questionnaire of the OPEX Benchmarking in 2010, p. 337.

(TPM) performance. The slight increase in „Preventive Maintenance" (enabler) linked with a significant increase of unplanned maintenance (performance), leads to the difficulties in deploying the TPM strategy in the industry. Also, companies were able to maintain the level of practice implementation but did not improve remarkably. In fact, an in-depth analysis of preventive maintenance showed that companies are setting the focus on technical aspects (e.g. checklists and documentation) rather than the empowerment of shop-floor employees (machine operators). Another point worth mentioning is the management of new technologies in the production environment. The category "Technology Assessment and Usage" did not reveal any improvements, i.e. it is not yet in the focus of most production managers. One could argue that the industry is in a state of stagnation concerning TPM.

TPM represents a manufacturing strategy for the effective usage of process technology. TPM is designed to efficiently manage fixed assets such as machines, equipment, and property throughout their life cycle. It does not only focus on the technical aspects such as the reliability of existing equipment and a careful selection of new technologies, but also the engagement of all employees in the production environment, from management level to shop-floor employees in maintenance-related activities. In OPEX programs, TPM is the basis for stable running machines and therewith forms the basis for further in-depth improvements in efficiency[4].

Due to high costs for maintenance (9 203 EUR per employee in 2009; employees include all people working full-time at the site, e.g. production, QA/QC, EH&S, IT, etc.[5]), one could assume that pharmaceutical companies had set a focus on this topic within the last five years. Maintenance costs, whether for internal employees or external specialists, represent a major part of the total costs within production sites. However, the analysis of practices implementation (enabler side) and corresponding key performance indicators (performance side) illustrated in Figure 1 draws a different scenario.

On the performance side, an increase in OEE for packaging of 15 % from 2004 to 2009 could be observed. However, an OEE of 51 % (median) in 2009 is not really outstanding compared to other process industries and their packaging processes. Various cross-industry studies show an OEE of 60 % for an average production site in the food and beverages sector. Pharmaceutical manufacturing still needs to catch up with regard to higher utilization in scheduled time, prevention of downtimes and avoidance of quality losses.

In fact, the availability of equipment and machines seems to be a problem for the industry as a result of direct stoppages and breakdowns. In 2004, the proportion of unplanned maintenance work as a percentage of the overall time spent for maintenance work amounts to 25 %. Five years later it has increased by 8 % to 33 % (median) for unplanned maintenance. It can be argued that most pharmaceutical companies struggle with the establishment of stable running manufacturing processes, which is caused by a low implementation of TPM enablers.

According to the OPEX model, three major principles of TPM on the enabler side can be distinguished: "Preventive Maintenance", "Technology Assessment and Usage", and „Housekeeping". Companies were able to slightly increase their level of „Preventive Maintenance" from 2004 (industry median of 71 %) to 2009 (75 %). Further, companies have installed formal programs on operational levels for maintaining their equipment and machines. Nonetheless, pharmaceutical companies still reveal shortcomings in TPM which they have not addressed

[4] See also Friedli and Goetzfried, In Retrospect: A Summary of Operational Excellence in the Pharmaceutical Industry in 2006 for a detailed description of the sub-system TPM (p. 18).

[5] Median numbers from the 2009 benchmarking.

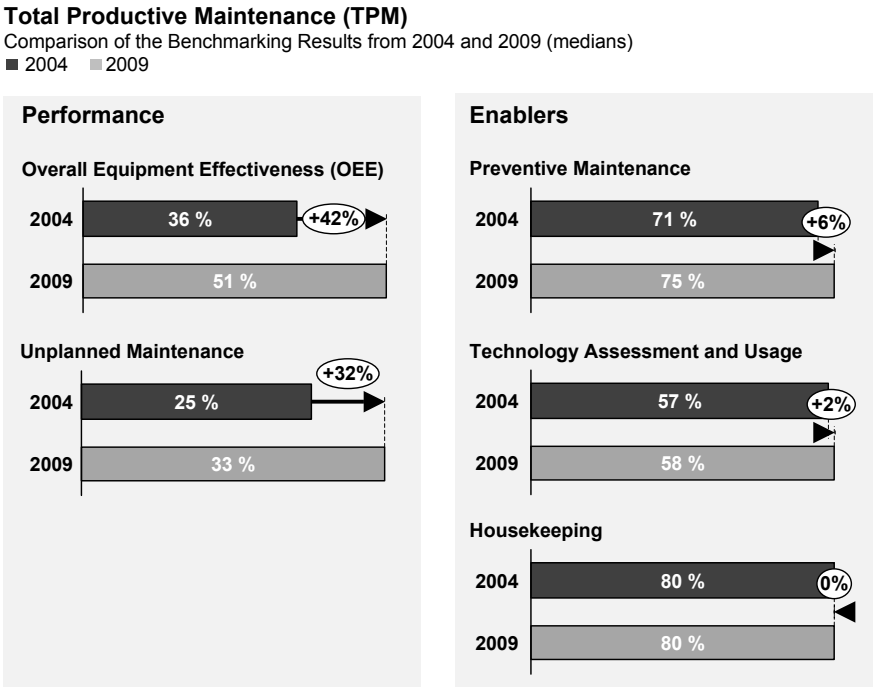

Figure 1: Total Productive Maintenance (TPM) – Results 2004 and 2009.

during these years. Especially practices pointing to autonomous maintenance by empowering shop-floor employees are not very common. Most maintenance tasks are still performed by maintenance specialists rather than by machine operators. In sum, maintenance systems in pharmaceutical companies are still reactive rather than foresighted, e. g. planning maintenance programs based on failure analyses.

The question remains if technology or equipment can be a source for strategic positioning. Other industries reveal that this can be the case, but to reach this some specific practices concerning assessment and selection at least have to be in place. For pharmaceutical companies this is still untypical. The 2004 analysis revealed that the pharmaceutical industry is very restrictive when it comes to the implementation of new production technologies. This might be caused by the fact that every change in the production process, including the usage of new technologies, needs to be approved by regulatory bodies. This category points to the screening of the market for new production technologies and the assessment of technical and financial benefit. More, it includes the effective use of new technologies. With 58 % in 2009 compared to 57 % in 2004, this category did not undergo any essential change, i. e. the industry is still lacking behind other industries with regard to the assessment and actual implementation of new production technologies.

A high score of 80 % in 2004 could be re-observed in 2009 for the category "Housekeeping". The vast majority of pharmaceutical companies have beholden their employees to keep their plant "neat and clean" and provide tools such as housekeeping checklists.

III The Best of Two Legacies: History, Present and Vision of the Roche-Genentech Operational Excellence Integration

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III.1 Genentech's Journey to Operational Excellence (2004–2009)

Colleen M. Griffith, Nick Rondoletto, and Fadel Hamed

In 1973, over sandwiches at a local deli, biochemist Herb Boyer and geneticist Stanley Cohen drafted the seminal experiment that lead to genetic engineering. By 1976, recombinant DNA was responsible for the birth of biotechnology and the founding of Genentech, Inc. By 2001, Genentech had developed one of the most sophisticated and advanced biotechnology manufacturing operations in the world, and by 2004, had launched four new products in 16 months and was granted FDA approval for its drugs Avastin (bevacizumab) and Tarceva (erlotinib).

In order to meet the anticipated demand for Genentech's products, the ever-growing pipeline, and a 30 % increase in the manufacturing workforce, the decision was made in late 2004 to launch Operational Excellence (OPEX) within Product Operations (PROP) at Genentech. The program's charter was to support growth within manufacturing by strategically creating continuous improvement capability and setting the stage for the Genentech Production System (GPS), which would leverage OPEX as an engine for ensuring planned, predictable performance.

III.1.1 The Three Phases of OPEX at Genentech

The OPEX program was to be rolled out in three phases; the "Foundational Phase" (2004), the "Stabilize Phase" (2007) and the "Transformational Phase" (2009). These three phases are illustrated in Figure 1.

In the Foundational Phase, the OPEX vision and strategy were developed. OPEX infrastructure was targeted at leadership capability, project execution, OPEX methodology, measurement and communication. Process improvement initiatives and projects executed during the foundational phase were characterized by their focus on building organizational capability, increasing productivity, improving plant utilization, and maximizing plant capacity.

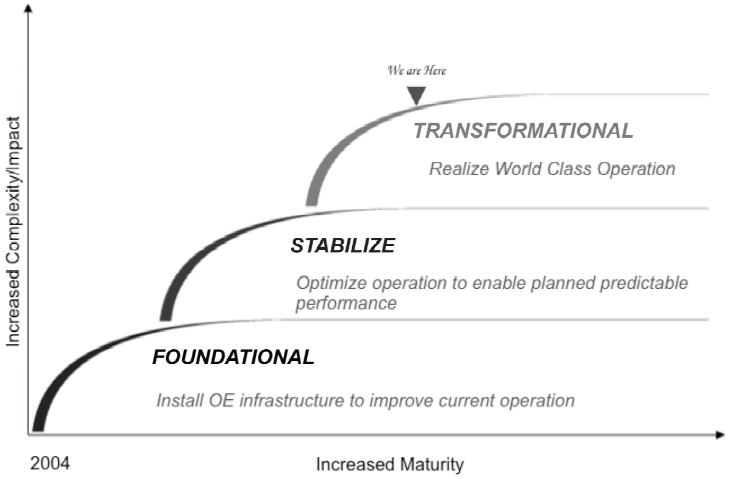

Figure 1: The three phases of OPEX at Genentech.

The Stabilize Phase of the OPEX program required a shift towards using the process improvement infrastructure to deliver planned, predictable performance. It was during this phase that the Class A journey, the GPS, and the Manage Operational Excellence (MOE) process were developed and introduced to optimize operations and deliver significant business results.

Finally, in the Transformational Phase, OPEX was being used to enable PROP's journey to world-class performance and the realization of its vision of being the most admired biotechnology production operation, respected for world-class innovation, regulatory capabilities, people development and operational excellence. In early 2009, the Roche Group acquired Genentech and, as a result, the Genentech Product Operations organization retired the PROP acronym and adopted the name Genentech Technical Operations (GT). During the transformational phase of PROP (GT), OPEX continued to be instrumental in providing a framework and necessary capability for the successful execution and realization of transformational change and successfully delivering integration synergies.

III.1.2 The Foundational Phase

The OPEX methodology in PROP (GT) was launched using Lean Six Sigma as a core methodology to deliver business results. In addition to the classical Lean Six Sigma training and project execution, effective process improvement programs like Kaizen, 5S, Visual Factory, and Total Productive Maintenance (TPM) were used to deliver significant business results. In addition to process improvement methodologies, PROP (GT) introduced change execution capability to successfully install and realize formulated strategies.

As shown in Figure 2, the OPEX program in PROP (GT) began with Lean Six Sigma training to produce process improvement practitioners and future leaders for the business. The training was originally conducted by third party firms but later transitioned internally to deliver the training. The internal training program developed and delivered a curriculum with four equally important courses, each with a different purpose and objective:

- OPEX for sponsors was an eight-hour course intended to teach project sponsors the characteristics of effective OPEX project sponsorship.

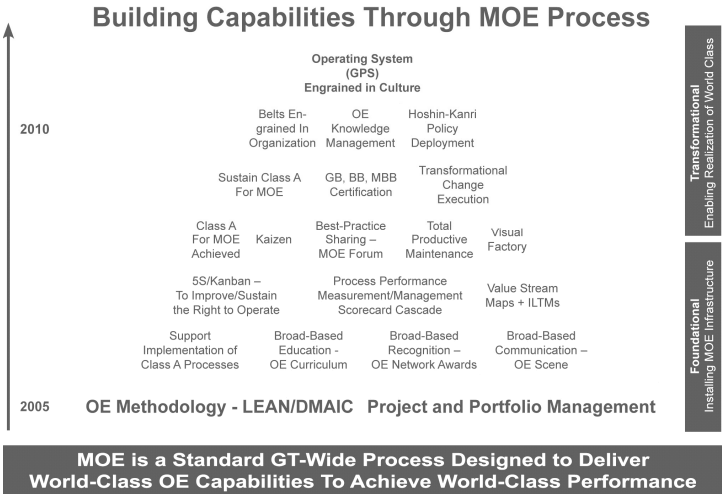

Figure 2: Building OPEX capabilities through the Manage Operational Excellence (MOE process.

- OPEX for team leaders was a twenty two-day course designed to provide OPEX practitioners the skills necessary to successfully lead and execute the Lean Six Sigma methodology during a current project.
- OPEX for team members was an eight-hour course designed to ensure that project team members have a basic understanding of OPEX execution principles.
- OPEX for everyone was a four-hour course delivered on demand to the business with the purpose of creating awareness for OPEX.

In just a few years, the OPEX education curriculum delivered thousands of hours of targeted instructions to thousands of Genentech employees across all functions and sites. The OPEX education curriculum successfully created OPEX capability and brand awareness and helped pave the way for the introduction of additional OPEX programs like 5S, Visual Factory, Kaizen and TPM. The curriculum has since evolved to include on-line, self-serve, short training modules so that employees can also learn in a self-paced environment.

III.1.3 The Stabilize Phase

The stabilize phase addressed the next steps on the stairway to excellence by focusing on planned and predictable performance. Class A, the GPS, and MOE process had been the key concepts of this phase.

Class A

As a critical first step for achieving world-class performance during the stabilize phase of the OPEX program rollout, the goal was established within the manufacturing sites to acquire Oliver Wight's Class A certification. To achieve and sustain Class A certification would show that PROP was able to deliver planned, predictable performance, proven through an objective, third-party benchmark that measured the sites' journey towards world-class performance.

II Making Operational Excellence Work – Training and Coaching Supporting Behavioral Change

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Summary

Almost all pharmaceutical companies work on small-scale to large-scale operational improvement projects. Over the past 10 years, Lean, along with Six Sigma, has ranked among the most prominent principles and methodologies supporting Operational Excellence (OPEX) strategies. However, according to our experience, many organizations have failed to achieve predicted and expected savings, or bring about sustainable success. One aspect is that training and coaching on how to foster behavioral change has not been properly addressed.

This chapter deals with the subject of training and coaching to avoid these pitfalls. At the same time it outlines the launch of an OPEX program in a global pharmaceutical company with numerous plants worldwide. It describes the ideal framework with regard to the deployment of the program, training and coaching, roles and responsibilities and of the different key players at different levels in the organization. It also emphasizes the importance of organizational learning.

(1) Building the Organization (see II.1 for a detailed discussion)

- Simultaneous or pilot launch?

  One issue that often arises is the question as to whether the program should be piloted or launched simultaneously. A pilot launch would give room for learning from the unpredicted and prepare for the roll-out in a real-life environment. For a simultaneous launch, it is crucial that everything is in place at the time of the launch so as not to lose credibility. When companies tackle the simultaneous implementation of a program, they usually achieve better and more sustainable results. However, substantial upfront investments have to be made, and unpredicted factors need to be anticipated.

- Starting the initiative and maintaining the momentum with good communication practices

  A better understanding of the starting point enables companies to determine what to focus on at the beginning of the program, and when to implement its various elements. This calls for a company-wide project management team with strong leaders[1] and good communi-

[1] See Crossman, Wyeth Pharmaceuticals – Transforming Culture, Delivering Results – Exploring the Operational Excellence Productivity Frontier, p. 120.

cation means. Communicating the initiative and its achievements is not only important in terms of steadily leading the organization in one direction, but also in terms of sharing knowledge. For knowledge sharing, a powerful IT solution is required.

(2) Training and Coaching (see II.2 for a detailed discussion)

- Proper sequencing of training across the organization

  Training must be sequenced properly to avoid confusion among staff. Also, training needs to be adjusted to the organization's operational and hierarchical layers and their different requirements. This is an absolutely essential item on the leader's agenda. Broadly themed, company-wide training programs designed to instill a culture of new ways of working and thinking are vital for the success of any OPEX initiative. It is easier to train employees in the technical aspects of an OPEX program than conveying leadership skills, and it can be done faster than making behavioral changes work. Technical solutions are objective, straightforward and visible, but behavioral changes can only be seen over time. If companies rush to implement a toolkit without ensuring that their employees (including managers) are prepared to understand its use and benefits, change will not happen. Simulation and learning factories are good means to support new toolkits.

- The design of a standardized training program

  It is advisable to develop a common and standardized training program for different levels of skill sets. Only standardized programs can ensure that a common language is „spoken" in the long run. However, the training itself should be provided in the local language whenever possible. This is particularly important for multinationally operating companies. For multinational companies, cultural diversity should also be considered. Therefore, it is extremely important to design a one-fits-all training program, execute the program and maintain standardization over the years to finally speak one worldwide corporate language.

- Involvement of senior leadership

  It is important to set up an appropriate organization supporting organizational learning, so that human energy is mobilized and people become willing and able to adopt new behavior. Senior leaders often delegate responsibilities to technical experts who may be well trained in technical skills. However, many of them lack leadership skills and are therefore not in a position to act as role models. Operational tools and approaches, the so-called „hard tools" need to be combined with „soft tools" such as interpersonal skills, coaching, and conflict management.

- Balance between technical (hard) skills and leadership (soft) skills

  Mastering soft skills means calling upon all employees to commit themselves to new ways of working and thinking. However, the technical skills required to embark on the new path must be mastered as well. Operations is the area that typically accounts for the largest number of employees with the greatest variety of skill levels.

(3) Sustaining Progress (see II.3 for a detailed discussion)

- New performance enhancing tools must replace existing performance tools

  The meaning of Lean and Six Sigma goes far beyond simply applying the tools. These principles entail a dramatic change in our ways of working. The aim is to establish a culture in which employees see opportunities everywhere and continually improve their processes. This calls for sharing knowledge in a learning organization. Communities of Practice (CoPs) can help to share the knowledge and accelerate learning.

- The development of internal subject matter experts, coaches and change agents

  Project leadership is important for keeping on track. At the heart of any operational improvement initiative, there are sufficient resources, although internal resources typically

need to be built up first with the help of external trainers. A well designed train-the-trainer program facilitates a quick start; however, experience should not be underestimated. Master Black Belts or Lean Masters should lead the program as subject matter experts and change experts in the day-to-day business. They are responsible for spurring new ideas and practices, and should act as champions for fostering the mindset of the continuous improvement process. The advantage of such an approach is to relieve line managers and leaders from the practical aspects of this task, while they still need to function as sponsors and process owners in the project execution. The responsibility for transformation initiatives cannot be delegated or outsourced. External experts play a vital catalyst role as teachers, coaches and consultants, but they cannot serve as role models. They may convey the new language, technical tools as well as interpersonal and leadership skills, but rarely stir the desire to change behavior. Organizational capabilities need to be developed in order to bring about permanent change.

- Leaders must become teachers

  Leaders must become teachers because companies tend to rely too much on external specialists. This may initially work when implementing, for instance, Lean. However, the responsibility should be transferred to those who are in charge of operations as soon as possible. For leaders this means adopting a new role and getting involved in coaching, training and supporting all activities which are part of the transformation including supervision, people management, technical and personal coaching. Managing performance must become everybody's responsibility.

(4) Benchmark Reality (see II.4 for a detailed discussion)

A recent research study conducted by the Institute of Technology Management, University St. Gallen investigated the reality with respect to the above. A health assessment, conducted by a company which introduced CoPs in their global organization reveals the level of acceptance of CoPs one year after the launch. It is evident that innovative solutions of knowledge management need time to become established.

II.1 Building the Organization

The OPEX program was launched by the CEO and the president of global manufacturing at the global leader's annual meeting. This was the starting point for putting a global OPEX organization in place. At its launch, the program was not designed as a cost cutting exercise, but was intended to increase quality by reducing process and product variation. Although Six Sigma was introduced as the number one problem solving tool, the program was neither launched as a Six Sigma, nor as a Lean program. Lean thinking became relevant much later after the Six Sigma methodology was established. The organization comprised several leaders, each responsible for one specific geographical area of the enterprise, e. g. North and Latin America, Asia and Africa and Europe. These leaders were organized as a group of peers with one informal leader. The leaders reported to the leadership teams of their respective area of responsibility. An OPEX leader was nominated for each site who reported to the site leadership team of the respective site.

The role of the area OPEX leaders was to

- implement plans to ensure a common understanding of OPEX fundamentals;

The Future of Pharmaceutical Manufacturing: Quality by Design and Operational Excellence Reinforcing One Another

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There is now a recognition that if quality can be designed or built into the product then that is to the benefit of both the manufacturer and the regulator. The manufacturer receives quick approval and operating flexibility within the approved "design space" and the regulator does not have to spend so much of its resources in reviewing and approving the documents and they are instead able to spend their resources on more value-added activities.

I.1 Three Generations of Quality Management Tools

To understand Quality by Design (QbD), one needs to first understand the evolution of quality in general. There are three generations of management tools fundamental to the evolution of quality activities that are widely accepted in the literature (Fan *et al.* 2008). "Quality by Inspection", as is widely practiced in the pharmaceutical industry today, is viewed as the first generation quality management tool. Inspectors remove defective products from production lines, or send them for repair or correction. In the era of mass production, however, said method is considered to be inefficient and cannot solve the problem from the root. The second generation tools, such as the Statistical Process Control (SPC) and Six Sigma, are characterized by the downstream approach to quality problems. They assist in achieving greater improvements in quality by preventing defects and reducing variations. However, they are still reactive in nature and address after-the-fact problem solving; the efforts of quality improvement are made at a purely manufacturing level. Some methods – such as the Failure Modes Effect Analysis (FMEA) that proactively approaches the quality problems – are generated and employed by project teams within the Six Sigma tool box to anticipate the failures, impacts, causes, and priorities, thereby minimizing the failures through actions in the early stages of manufacturing.

The third-generation tools, on the other hand, are aimed at more actively detecting and solving quality problems from the earliest stages of product development and product planning. Typical examples of third-generation tools are Quality Function Deployment (QFD) and QbD.

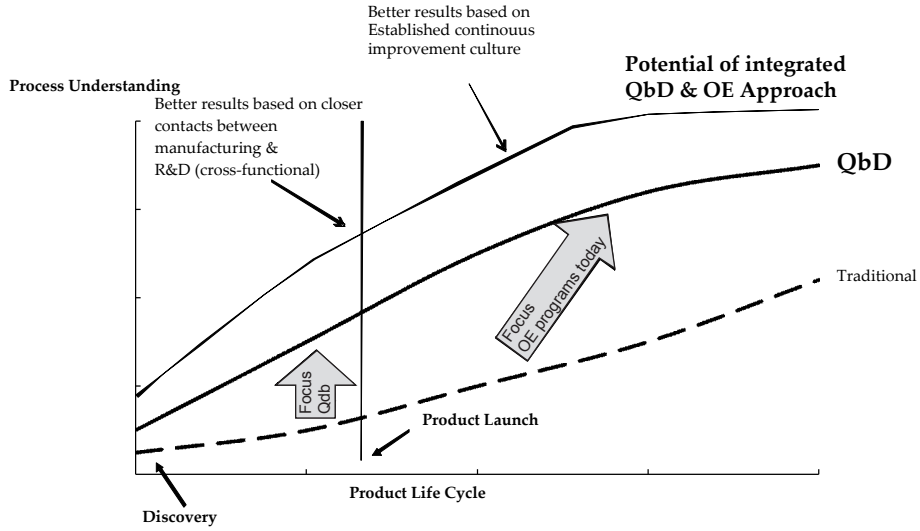

Figure 1: QbD and its potential contribution to OPEX (OE = Operational Excellence).

The concept of building customers' requirements in the final product is not a new idea, but the third-generation tools of quality activities enable a realization of this concept by using a structured and methodical manner. Product objectives are achieved with improved quality, lower cost, and greater customer satisfaction.

There is a potential advantage of implementing QbD in the early stages of product development rather than waiting for the product to be approved and marketed. QbD principles also integrate extremely well with the principles of achieving operational excellence. Figure 1 is a schematic of relative advantages of implementing QbD early in research and development and its overall impact to Operational Excellence (OPEX).

I.2 Quality by Design

Pharmaceutical companies are pushing ahead to evolve in quality (Figure 2). The FDA and industry agree on the so-called "desired state" for pharmaceutical manufacturing. The definition of "desired state" in pharmaceutical manufacturing is (Nally and Karaim 2007):

1. Product quality and performance achieved and assured by design of effective and efficient manufacturing processes.
2. Product specifications based on mechanistic understanding of how formulation and process factors impact product performance.
3. An ability to effect continuous improvement and continuous "real time" assurance of quality.

It is suggested that one can get to the desired state by using QbD. As discussed earlier, QbD is different from traditional quality activities which focus on improving existing products and processes using statistical process control. QbD refers more to design of new products or redesign of existing products as if they were being looked at anew. QbD as defined by Hus-

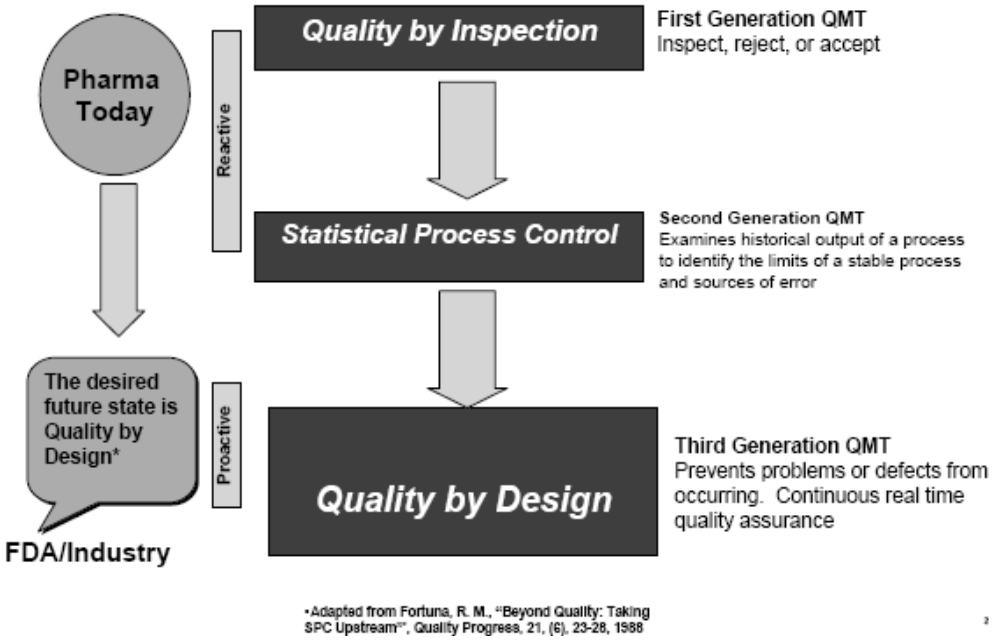

Figure 2: Pharma companies are pushing ahead to evolve in quality (QMT = Quality Management Tool).

sain (2005) as "A systematic process of defining optimal design specifications of a product, its manufacturing process and its quality control and assurance methods." However, this can only be achieved with the following:

1. A high degree of process understanding.
2. High confidence of low risk of releasing a poor quality product, and
3. Maintenance of high efficiency through continuous learning and improvement.

QbD in pharmaceutical product development and manufacturing may be defined as designing and developing formulations and manufacturing processes to ensure predefined product quality (Yu 2006). It consists of four steps:

1. Define a Quality Target Product Profile (QTPP) or define product quality attributes.
2. Design and develop the product and manufacturing processes necessary to meet the QTPP.
3. Identify and control critical raw material attributes, process parameters, and sources of variability.
4. Monitor and adapt these processes to produce consistent quality over time.

Conventional quality tools such as QFD can provide a means to determine Critical-to-Quality (CtQ) criteria, which customers are most able to support. QFD tools such as the affinity diagram, fishbone diagram, and the "house of quality" can be used to define and prioritize these CtQ's.

The ultimate goal of QbD is to develop a robust process. Robust process is the ultimate "desired state". The most appropriate definition of robustness, as described by quality guru Dr. Taguchi,