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EXPERT REVIEW

Statistical Thinking and Knowledge Management for Quality-Driven Design and Manufacturing in Pharmaceuticals

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ABSTRACT The purpose of this article is to present the evolution of quality principles and how they have been implemented in the pharmaceutical industry. The article discusses the challenges that the FDA PAT Guidance and the ICH Q8, Q9 and Q10 Guidelines present to industry and provides a comprehensive overview of the basic tools that can be used to effectively build quality into products. The principles of the design of experiments, the main tools for statistical process analysis and control, and the requisite culture change necessary to facilitate statistical, knowledge-based management are also addressed.

KEY WORDS design of experiments · knowledge management · process analytical technologies · process variability · quality · quality by design · statistical process control and analysis · statistical thinking

INTRODUCTION

There are a number of challenges currently facing the pharmaceutical industry, which are driving the changes presented in this article. These include decreasing R&D productivity, patent expiry issues and thus increased generic competition, in addition to the emergence of competitors from the East. The current regulatory climate also has increased expectations of the product attributes, and there is progressive narrowing of the window of exclusivity to novel medicinal products. These are all within the current context of an economic downturn. Furthermore, the complexity of medicinal products is expected to increase in the future with the use of technologies such as novel drug delivery systems, advanced therapies such as gene therapy, and, ultimately, individualised medicines.

Several publications (1–4) have highlighted the deficiencies in current pharmaceutical manufacturing and the need for a change in paradigm in order to address the unmet expectations of performance in this area. These changes would contribute to tackling the competitive challenges that the pharmaceutical industry is facing and ultimately deliver higher quality medicinal products to patients.

In order to facilitate and encourage the early adoption of new technological advances and the implementation of modern quality systems that would increase manufacturing efficiency by the pharmaceutical industry, the FDA launched in 2002 the "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century" initiative (3), part of which was the Guidance to Industry on Process Analytical Technology (PAT) (4).

At a wider level, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) that brings together Europe, Japan and the United States has adopted three guidelines that support the change in paradigm, namely ICH Q8 on Pharmaceutical Development (5), ICH Q9 on Quality Risk-Management (6) and ICH Q10 on Quality Systems (7). ICH Q8 introduces the concept of Quality by Design (QbD), the main principle of which is the

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acknowledgement that quality cannot be tested for in products, but should be built-in, by design. QbD is a systematic approach to pharmaceutical development that emphasises product and process understanding as well as control, which is based on sound science and quality risk management. These three guidelines create a framework that allows flexible regulatory approaches in review and inspection, when industry can demonstrate that a systematic and in-depth understanding of the product and the process has been achieved, coupled with an appropriate quality system.

The purpose of this article is to discuss the main concepts of quality and how they can be used by the pharmaceutical industry in order to improve pharmaceutical development and manufacturing, as well as the potential pitfalls resulting from a narrow interpretation and implementation of the above mentioned regulatory initiatives and guidelines. Moreover, it addresses the need for the routine use of statistical tools and the adoption of systematic approaches to ensure that the flow of information and creation of knowledge are properly integrated throughout the organization.

DEFINITION OF QUALITY

The dictionary offers several definitions of the word *quality* and several quality gurus have given their interpretations. The problems inherent in defining the quality of a product have been highlighted by many authors. Pirsig (8) suggested that "quality is a characteristic of thought and statement that is recognised by a non-thinking process. Because definitions are a product of rigid formal thinking, quality cannot be defined." The difficulty in defining quality is to translate future needs of the user into measurable characteristics so that the product can be designed to satisfy the user and also be affordably priced (9). As proposed by Feigenbaum (10), a crucial role of top management is to recognise this evolution towards a customer-driven definition of quality at different stages of product growth.

Quality also has a multidimensional aspect, which was highlighted both by Montgomery (11) and Deming (12), who stated that it is virtually impossible to define quality in terms of a single characteristic. Garvin (13) provided an overview of the key points concerning the different dimensions of quality: performance, reliability, durability, serviceability, aesthetics, features, perceived quality and conformance to standards. Hoyer and Hoyer (9) have categorised the definitions of eight quality gurus into two levels:

Level 1: Quality is a simple matter of producing goods or delivering services whose measurable characteristics satisfy a fixed set of specifications that are usually numerically defined (quality of conformance, independent of the customer)

Level 2: Quality products and services are simply those that satisfy customer expectations for their use or consumption (quality of design, dependent on the customer)

In short, the Level 1 definition focuses on meeting specifications, while Level 2 targets customer satisfaction. The definitions provided by Shewhart, Ishikawa, Feigenbaum and Deming fall in the Level 2 category, while Crosby supports the Level 1 approach, defining quality as conformance to requirements. Finally, Juran balances both Level 1 and Level 2 by defining quality as fitness for use and freedom from deficiencies (9).

In the field of pharmaceuticals, definitions for quality are presented in two ICH guidelines. ICHQ6A (14) follows Juran's approach about fitness for use, while ICH Q9 (6) is in line with Crosby's approach as fulfilment of requirements.

The two aspects of quality mentioned above are also reflected in the definition provided by the American Society for Quality (ASQ). In accordance with ASQ (15), "quality can have two meanings: a product or service free of deficiencies and the characteristics of a product or service that bear on its ability to satisfy stated or implied needs."

The limitation with the first level definition is that it lacks the dynamic to address the changing needs of the customer. The product may meet the specifications, but at the same time it may not satisfy customer needs, which are continuously changing, while the specifications remain constant or change at a much slower pace. On the contrary, the Level 2 definition clearly states that meeting customer needs is the ultimate goal and that the specifications are meaningful only when they are reflecting these needs at the technical level. According to Ishikawa (16), one simply cannot design a good product or service if it is not known what "good" means to the customer, and thus the designer must create a map that moves from the world of the customer to the world of the designer (17). Thus, quality reflects how well the engineer has translated the customer needs into the physical characteristics of the product (18).

Moreover, and as Montgomery argues, quality is not a problem that can be dealt with downstream by "gold plating" the product or by solving manufacturing problems on a case-by-case basis (band-aid solutions). Instead, quality can be planned, and it should be built into the product by design, as stated by Juran who first introduced the concept of Quality by Design (QbD) (19). As mentioned above, setting and meeting specifications could be considered meaningful as the next sequential step. This step has the obvious prerequisite that the engineer has designed a robust process which will produce a product or service complying with the set specifications, whilst the variability of the desired quality characteristics should only be attributed to chance causes. As Deming has pointed out, "our aim in

production should be to improve the process to the point where its distribution is so narrow that the specifications are lost beyond the horizon" (20). Therefore, Montgomery (11) proposed a more technical definition for quality according to which "quality is inversely proportional to variability."

THE EVOLUTION OF QUALITY

This section will briefly describe the evolution of quality culture from just reacting to inspection events towards utilising engineering principles to build quality into the product (17). The major milestones (21,22) in the evolution of quality are depicted in Fig. 1.

In the early 1930s, Shewhart recognized that industrial processes yield data that could be analyzed using statistical techniques to check whether a process is in control and thus stable, or if it is affected by special causes that should be identified and removed. This was the foundation of control charts, which are a statistical tool widely used in assessing whether the process variability is only due to chance causes. Shewhart could be considered among the first who clearly described the causal relationship between process variability and finished product quality, which means that the latter depends on the process that created it. Shewhart's control charts combined with the use of process capability indices, which assess whether the process is capable of meeting the set specifications (23), provide a very good insight of process performance (24). The importance of the statistical process mapping has been highlighted by Deming in the following quote: "There is no process, no capability and no meaningful specifications, except in statistical control" (12).

W E. Deming, a statistician with the U.S. Department of Agriculture and Census Bureau, progressed the work of Shewhart and became a leader of the quality movement both in Japan and in the United States. One of Deming's main beliefs was that quality improvement requires, above all, management commitment and action, which will then motivate the workforce. His approach is well-documented in his 14 points directed primarily to the management (12) and could be summarised as follows: emphasis on change, institution of leadership, driving out fear from the workforce, breaking down the barriers between departments, elimination of numerical targets and slogans, need for continuing education, elimination of the need for inspection on a mass basis by building quality into the product in the first instance and continuous improvement of the production system. All the above points should be driven by management, who should lead the change. According to Deming, real quality improvement is not possible without profound knowledge (25), which requires in-depth understanding of the following closely interrelated elements: systems approach, theory of knowledge, understanding of variation and psychology. In short, Deming proposed a systematic approach for continuous improvement, and his teaching balances both the human dimension and the technical aspects of quality.

Juran had the same viewpoint to Deming with respect to the responsibility of management in attaining quality. They both shared the belief that management is responsible for approximately 80% of the opportunities for quality improvement, while the workforce only for the remaining 20% (11).

The teachings of Shewhart, Deming, Juran and other quality gurus influenced greatly the way industry perceived

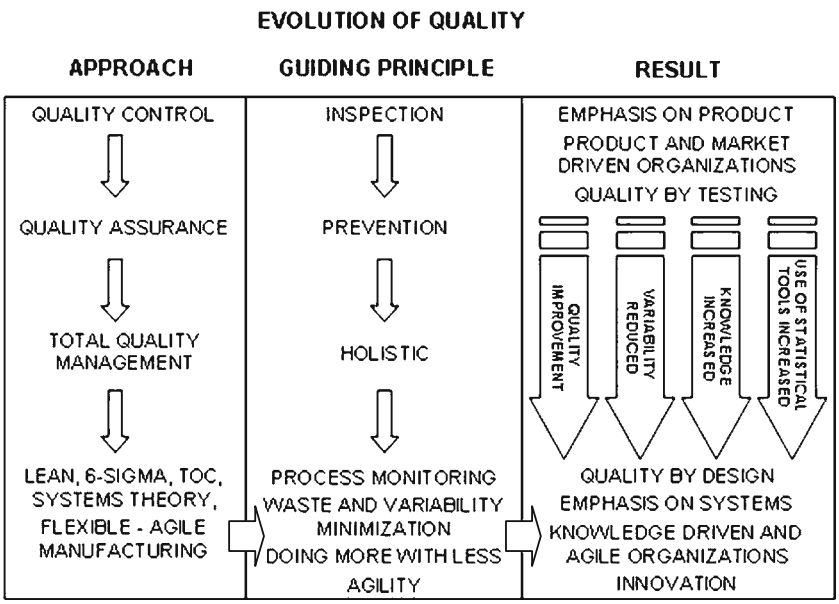

Fig. 1 Major milestones in the evolution of quality.

quality, but the full adoption of their concepts was gradual. Until World War II, product quality was tested via unit-by-unit inspection for conformance to requirements. The same approach was retained during the war; however, the increased volume strained the existing quality testing systems; thus, acceptance sampling was introduced. The above phase represents the framework of quality control in its narrow view based solely on inspection.

It was in Japan, however, where most notably the seeds of the next quality paradigm were sewn most strongly. After the end of World War II, Japan, earlier than any other country, implemented processes based upon the views of the American quality gurus like Juran and Deming and the Japanese engineer Kauru Ishikawa. Therefore, in the early 1950s the functions of the quality control operation expanded beyond simply checking the final product quality control, giving way to quality assurance, which signalled a major cultural change departing from the narrow, product-focused approach to emphasizing preventive actions. In other words, there was a transition from "find and fix or reject" to "prevent" (17). Soon this paradigm evolved further to include not only manufacturing, but all organisational processes and the associated staff, giving birth to the "Total Quality" approach, which in the USA was named Total Quality Management, again emphasizing the total, i.e. the holistic aspect of quality. Feigenbaum with his book on TQC, Oakland with his work on TQM (26) and other researchers (27,28) have introduced and further developed the concept that everybody in an organisation is responsible for quality. The term TQM was coined by the US Naval Air System Command in the early 80s and was particularly widespread thereafter. TQM is "a strategic integrated system for achieving customer satisfaction that involves all managers and employees and uses quantitative methods to continuously improve an organization's processes" (15).

In summary, as shown in Fig. 1, the evolution of quality involved a significant mind-set transition from product focus to process and systems focus (21,29), since the first is a dependent outcome of the latter. The following key words represent how quality was regarded through the years: inspection, prevention, holistic and the systems approach. The main pillars for this transition were systems and knowledge theory, consideration of all employees' involvement, psychology and statistical tools for understanding variability and process monitoring.

A process, as defined in ISO 9000:2000 clause 3.4.1, is a set of interrelated or interacting activities that transforms inputs into outputs. Inputs to a process are generally outputs of other processes. Processes in an organisation are generally planned and carried out under controlled conditions to add value. A process should be goal-oriented, systematic, capable and legitimate (19).

According to Montgomery (11), the inputs of a process may be controllable factors, such as temperature and feed rates, or uncontrollable/difficult to control inputs, such as environmental factors. The output of a process has several quality characteristics, which are a measure of its quality. The objective of each process is to consistently provide products of the intended quality characteristics. A schematic diagram of a process as described above is depicted in Fig. 2.

One of the most important aspects of the year 2000 ISO revisions for ISO 9001 and ISO 9004 was the adoption of the process approach to Quality Management Systems (30).

The systems theory provided the scientific grounds on how processes should be viewed. A system is a complex of interacting elements that work together to accomplish its aim (31). Thus, a process can also be considered as a system of interrelated causes which produce a specific output. ISO 9001: 2001 recognises that the entire system is made up of interrelated processes, so, in addition to consideration of the processes for product realisation, one must identify and manage the processes for the whole system (32). The real power of the system lies in the way its components come together and are interconnected to fulfil its purpose. Deming (25) identified early on the importance of systems theory as an integral part of his profound knowledge concept; thus, in his fifth point to management, he urges constant improvement of the production system in order to improve quality and productivity, thereby constantly decreasing costs.

Systems thinkers view quality performance with a holistic approach. They focus on the whole, paying attention to the interactions between the parts rather than the parts themselves (33). As Ackoff (34) pointed out almost half a century ago, any attempt to understand a system by

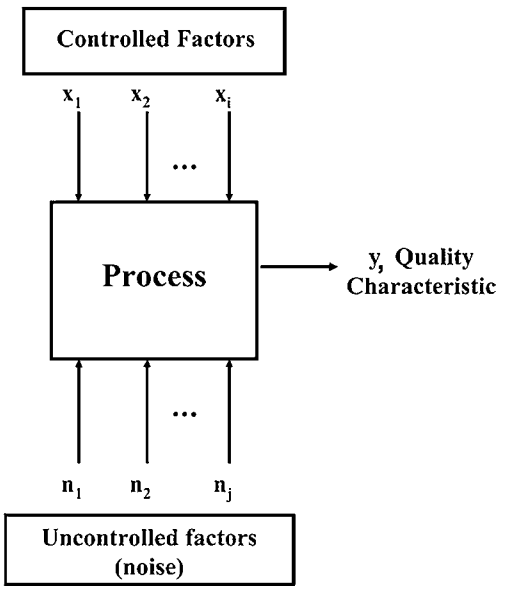

Fig. 2 Schematic diagram of a process and its variables (factors).

focusing only on its components and not taking into account their interactions is deemed to fail, since in systems theory the whole is more than the simple sum of its parts. Therefore, an organisation must identify its components, but more importantly should manage their interactions, since the latter are vastly responsible for the characteristics of the system's output. The key points of systems thinking as summarised by Prevette (33) are

- more attention to interactions than components
- more knowledge of statistical variation than of discreet numbers
- more long-term than short-term focus
- more cooperation than fear, blame and internal competition.

The holistic view of industry operations as a system of interrelated processes and the latter as sub-systems of interacting factors is fundamental in building quality into the product and thus achieving Quality by Design. However, the systems approach has been adopted in pharmaceuticals only in the early 2000s through the FDA regulatory framework "Quality Systems Approach to Pharmaceutical cGMPs" and the ICH Q10 Guideline on "Pharmaceutical Quality Systems."

At the beginning of the 21st century the quality concept has moved beyond the manufacturing sector into such areas as healthcare (35,36), education (37) and government (38), and the approach to quality evolved further. An example of this evolution is Six Sigma (39), a methodology developed by Motorola to improve its business processes by minimising defects at the lower possible level. Six Sigma addresses the need to reduce further variability and increase process capability and thus production efficiency. Another example is the Lean Manufacturing approach, which focuses on eliminating all waste in manufacturing processes. This concept, which is based on the Toyota Production System is also characterised by optimum automation, "just in time" supplier delivery disciplines, quick changeover times, high levels of quality and continuous improvement (15). In lean systems, the product is produced at the pull of the customer in pursuit of perfection.

Finally, the theory of constraints (TOC) as popularised by E.M. Goldratt and J. Fox (40) helped to further advance the approach to quality. TOC considers that the performance of any system is controlled by its weakest link; thus, by focusing and managing effectively this bottleneck, the systems output is improved. Despite the fact that the above briefly presented concepts and practices for quality improvement have been developed separately, they should not be considered in isolation, since they have shown significant synergistic effects, when integrated (41). As pointed out by Kovach *et al.* (42), a major competitive advantage can be achieved if Six Sigma, Lean Manufacturing and agile manufacturing are used in combination to improve quality, flexibility, responsiveness and innovation, while minimizing cost.

Today's environment presents many challenges, including globalisation, green policies, rising energy costs, information technology, knowledge management, web-based services and individualised customers needs. It remains to be seen how the above-mentioned trends will affect the quality paradigm in the near future for the whole business sector and more in particular for the pharmaceutical industry.

THE PHARMACEUTICAL INDUSTRY IN THE BEGINNING OF THE 21st CENTURY

The pharmaceutical industry is a process industry, which, in contrast to other similar industries like petrochemicals, polymer and chemicals (43), is still relying on end-product testing and inspection to test quality. Shanley and Thomas (44) point out that although the pharmaceutical industry faces a "sea change," and, as many have already suggested, its manufacturing operations need to become more agile, its response has been quite limited, since facilities have not become automated, plants still have "lights out," continuous manufacturing is still relegated to specific niches. Whilst PAT and QbD have not started a revolution, they are gradually applied or at least studied by some companies.

The necessity of creative thinking and innovation in the pursuit of quality is clearly explained by Plsek (45). The Satellite Process Assurance Hub (SPAH) mini smart plant (46) already patented in the USA and the FlexFactory (47) bio-manufacturing platform are examples of innovative manufacturing plants that incorporate lean features and facilitate the application of QbD and PAT. However, cases like the examples mentioned above are only exceptions to the rule, since most of the pharmaceutical industry lies idle (44).

There is still an established four-step sequential process of producing medicinal products, which consists of the following stages: manufacturing, quarantine, testing and release to the market. This practice involves raw and in-process materials testing, manufacturing in accordance to an already approved fixed process and final testing of the finished product to check if it meets its predefined characteristics. In all cases the test for defects or defective products is performed "after the fact" at the end of the manufacturing process or after one of its steps. This inspection practice is also referred to as Quality by Testing (48).

The problem with testing product quality "after the fact" is that it is based on inspection of the final outcome; thus, when a failure is observed, defective products have already been produced, and the cost of poor quality in terms of

scrap, rework or warranties is increased. As pointed out by Antony and Taner (49), inspection is an expensive, unreliable and non-informative activity, since it is reactive and does not give answers as to why the error occurred and how it can be corrected. In addition, inspection does not guarantee that a defective product will not pass the test, and this is a reason for a number of recalls from the market. In the same line of thinking, Goh (50) has noted that inspection and testing merely detect defective product units and prevent them from going downstream to the next process or customer. This approach does not facilitate quality improvement. Instead, it is much better to focus on the upstream process, which has produced the product in the first place. This has been also highlighted by W.E. Deming in the third out of his 14 points: "cease dependence from mass inspection." When a product leaves the door of a supplier, it's too late to do anything about its quality. Quality comes not from inspection, but from improvement of the production process. Quality cannot be inspected into a product;' it should be build in the product by design, as was also clearly indicated by Juran (19).

Companies initially relying on Quality by Testing and then switching to Six Sigma practices realised that about 80% of the quality problems they were fixing could be mitigated in the design phase (17). The financial benefit of managing the cost of quality should not be overlooked, since as DeFeo (51) claimed, the cost of poor quality contributes as much as 15–30% of all costs.

In practice, however, it is not possible to produce identical units after repeating the process several times (11). The difference between individual outputs of a process is called *variability*. All processes are subject to variability (19) coming either from common causes inherent to the process on a regular basis, also referred to as *natural variation*, or from special causes, which comprise the unnatural portion of variability and can be attributed to atypical events or changes to the regular process (52). Sources of variability in a manufacturing process can be the people, equipment, materials, methods, environment and measurement systems (53,54). A process operating under the effect of common causes only is said to be under statistical control, i.e. it is stable and predictable or, as originally stated by Shewhart, "a constant system of chance causes" (18). Statistical Process Control (SPC) tools and especially controls charts are useful diagnostic means to determine the status of a process, since the nature and extent of this variability are critical input to process design and, therefore, need to be taken into account. Process designers, who lack this information, may be able to develop a process that works under laboratory conditions but not necessarily under real operating conditions. Process variability is a major cause affecting production lead times, product and process costs, process yields, and, ultimately, customer satisfaction. Deming identified variability as "a disease that needs to be treated" (55), while others have stated (50,56) that practically all quality problems in manufacturing of goods or provision of services have namely one cause: variability. Unfortunately, although the importance of variability in process and product design has been identified very early and investigated quite thoroughly, uncontrolled variability is still a major problem for the pharmaceutical industry, as stated by FDA in the PAT Guidance (4).

According to the AMR report (2) "Pharmaceutical Quality: Build it into the Process," the industry average for both rework and discarded product is 50%, on hold product inventories are at the 40–60 day level on average, plant utilisation levels run at 40–50%, average cycle times are in the 30–90 day range and laboratory bottlenecks can add as much as 75% to the cycle time. The bottom line of the report is that "reducing cost and cycle times requires pharmaceutical manufacturers to take variability out of core production processes with an integrated approach to Enterprise Quality Management." An integrated approach across operations is key to achieving the desired process performance. Unfortunately, however, currently there is a poor flow of knowledge between the different Pharma operations, i.e. clinical, commercial, quality and regulatory. It has been reported (57) that the pharmaceutical industry suffers from the so-called data rich/information poor (DRIP) syndrome. It is document-centric and fails to integrate or align business and information processes or create the necessary framework to transfer business, science and compliance data across organisational silos. Moreover, while the amount of information that pharmaceutical companies generate and collect during drug development doubles every 5 years, only 10% of this information is ever leveraged to improve overall competitiveness and compliance.

The emergence of e-manufacturing has revealed more limitations in industries regardless of their type, such as plants isolated from the rest of the organisation, still operating with in-house-made systems for plant floor control, production planning made to stock, sales and marketing being the major concerns without recognising that supply and demand are usually quite variable, while production processes are designed for long runs with no flexibility to address customization (58).

All the shortcomings of Pharma manufacturing discussed above have been acknowledged by FDA in its cGMP for the 21st century initiative report (59) with a clear call for action. According to this report, the processes are static, the functionality of the material characteristics in relation to the process is not well understood, out-of-specification values occur frequently, there is variability in the measurement systems, a difficulty in differentiating between inherent and special causes variability is observed, and the information

needed for continuous improvement is segregated in different departments.

FDA PAT GUIDANCE, ICH Q8-10

The need to change the currently established paradigm in pharmaceutical operations has been acknowledged by FDA. For this reason, the cGMP for the 21st century initiative was launched in August 2002 with the scope of accelerating the public health benefits from modern methods to produce more precise, effective medicines and assure their quality. The objectives of this initiative were to encourage the early adoption of new technological advances and quality systems approaches by the industry, to promote the implementation of risk-based approaches that focus both industry and Agency attention on critical areas, and to ensure that regulatory policies are based on state-of-the-art pharmaceutical science (60).

Part of the FDA's cGMP initiative was the Guidance for Industry on Process Analytical Technologies (PAT) (4), which describes a regulatory framework that encourages the development and implementation of innovative approaches in pharmaceutical development, manufacturing, and quality assurance. The Guidance acknowledges that in recent years significant advances have taken place in engineering, quality management systems and risk management, providing modern tools that can be used to ensure manufacturing quality. Such new tools enable manufacturers to detect, analyze, correct, and prevent problems and continuously improve their manufacturing processes. The guidance facilitates the introduction of new such technologies to improve the efficiency and effectiveness of manufacturing process design and control and quality assurance.

The move towards science-based development and manufacturing was embraced at an international level by ICH. In 2003, ICH parties published a consensus vision statement to "develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science." Since then, ICH has developed three guidelines that support this vision, namely ICH Q8 on Pharmaceutical Development, ICH Q9 on Quality Risk-Management and ICH Q10 on Quality Systems.

ICH Q8 acknowledges that in all cases a product should be designed to meet patients' needs. If the applicant chooses to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters, then it is possible to develop risk-based regulatory decisions that facilitate manufacturing process improvements and reduction of post-approval submissions. The concept of Quality by Design (QbD), as introduced by Juran (19), is for the first time presented in a regulatory guideline in ICH Q8, where it is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. ICH describes elements that can be used in the QbD approach. The applicant should first define the quality target profile of the product and then identify the critical quality attributes (CQAs), i.e. the physical, chemical, biological or microbiological properties or characteristics of the finished product that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Then, the "critical few," according to the Pareto principle (19,61), material attributes and process parameters that have a significant impact on product CQAs, should be identified together with the functional relationships that describe their effect on CQAs. This can be accomplished by using prior knowledge, experimentation and risk assessment. The understanding of the process can be useful in risk assessment and risk reduction through the development of an appropriate control strategy that would enable real-time monitoring and control of the product and possibly real-time release testing. Such a systematic approach would facilitate continual improvement and innovation throughout the product lifecycle.

ICH Q8 provides a basis for risk mitigation through the in-depth product and process understanding gained in pharmaceutical development, while ICH Q9 develops the principles and some of the tools of quality risk management, which is a systematic process for the assessment, control, communication and review of risks of the quality of the medicinal product across the product lifecycle. An effective quality risk management approach can further ensure the high quality of the medicinal product for the patient by providing a proactive means of identifying and controlling potential quality issues during development and manufacturing. Additionally, the use of a quality risk management system can improve the decision-making when a quality problem arises and enables more effective and consistent risk-based decisions, both by regulators and industry.

ICH Q10 complements ICH Q8 and ICH Q9. An appropriately designed process needs to operate in a suitably designed plant managed by an effective quality system. ICH Q10 establishes a model for a pharmaceutical quality management system that would facilitate innovation and continuous improvement throughout the product lifecycle and would strengthen the link between development and manufacturing activities. The main pillars of such a system are knowledge management and quality risk management.

The PAT Guidance and ICH Q8, Q9 and Q10 create a regulatory framework that encourages science-driven and

knowledge-based development and manufacturing, whose expected benefits would be (59) assured acceptable end product quality with the possibility of real-time testing, improved efficiency through variability understanding and management and, thus, reduced cycle times, less scrap, rework, rejects and reprocessing, reduced energy and material use and increased capacity. Well-understood processes are also easier to automate and operate in a continuous manner.

The above benefits would translate into significant cost savings. The cost of poor quality has been widely discussed. As Juran stated, "in the United states close to a third of the work done consisted of redoing what had been done before." Depending on the industry, the cost of poor quality was responsible for 20–40% of the total effort (62). In the field of pharmaceuticals, the world-wide cost savings from the efficiency improvement of manufacturing processes has been estimated to be as high as US $90 billion, which is equivalent to the current cost of developing 80–90 new medicines every year (59).

Process understanding also facilitates product transfer between manufacturing sites, since it allows a better estimation and control of the scale effects. In today's global environment, this is particularly important, since in many cases medicinal products need to be transferred from one site to another at some stage of their development or manufacture. Furthermore, mergers, acquisitions, the ongoing rationalisation of manufacturing, and other factors have increased the frequency with which pharmaceutical manufacturing organizations must effectively and efficiently transfer products and manufacturing processes from one location to another (63).

Application of the Regulatory Guidance

Despite the urgent need and the evident benefits from shifting the pharmaceutical development and manufacturing practices from inspection and oversight towards a knowledge-based management of processes that will be capable of providing a higher level of assurance for product quality, it seems that a part of industry has a narrow interpretation of the regulatory guidance discussed above (64). There is some criticism that implementation efforts are focusing on the application of on-line analytical technology as a replacement for off-line laboratory testing, rather than on understanding control and reduction of variability (64). Whilst this approach will provide potentially some time and cost savings by reducing laboratory testing, there is no real change in the existing manufacturing practices, since the above-mentioned limitations (59) are not adequately addressed. The focus should not be on the use of advanced sensors for online quality control, but in understanding the process, developing a risk-based and integrated systems approach, which constitutes what Maes and Liedekerke (64) defined as a broader view. As stated by A. Hussain (65), "PAT is not about just throwing in-line sensors at a production line. It is more about understanding the sources of product variability during production and controlling processes in a flexible way to allow you always to produce a quality product."

In light of the above, interesting data were presented as part of the Pharmaceutical Manufacturing Research Project by Marcher and Nickerson (66), which is a preliminary benchmarking study of 42 facilities from 19 pharmaceutical companies including process development, active pharmaceutical ingredients and finished product manufacturing. The authors, recognising the different trends in applying the regulatory guidance, investigated, amongst others, the usefulness of PAT data analysis tools such as Design of Experiments (DoE), PAT analytic tools such as process analysers and PAT monitoring tools including process monitoring, control and end-point tools. The findings showed that PAT data analysis tools increase yield over time, while PAT analytical and monitoring tools have a variable, sometimes negative, link with some manufacturing performance indicators, e.g. cycle times. A possible explanation for the latter could be that they might be superior in identifying deviations and thus trigger future process improvements. Despite the statistical limitations referred to in the study, it can be assumed that higher levels of performance indicators could be obtained when analytical and monitoring tools are combined with PAT data analysis tools, which generate the necessary process knowledge.

Possible reasons for the narrow interpretation of the regulatory guidance are as follows (64):

- Implementation projects often lack a multidisciplinary approach and operate within the existing organisational boundaries.
- There is a lack of company-wide commitment, since the business benefits of improving quality are not well understood and are often estimated on a short-term basis.
- There are knowledge gaps in implementing QbD and PAT, and, thus, industry is reluctant or uncertain of how to implement experience from other industries which are more advanced in this field.

ENABLERS FOR THE DESIRED STATE

The enablers to reach the desired state can be divided into two categories: statistical thinking, with its tools, and the concept of knowledge management in a company-wide culture of continuous improvement and innovation.

Statistical Thinking and Tools

Statistical thinking is a learning and action approach based on three fundamental principles: all work occurs in a system

of interconnected processes, variation exists in all processes, and that understanding and reducing variation are keys to success (67). In a more general sense, the core elements of statistical thinking are generation of data, extraction of relevant information from these data and utilisation of this information for optimal decision-making (68). Understanding systems and processes, as well as monitoring and reducing variation, i.e. the main aspects of statistical thinking, constitute the basis for achieving Quality by Design. The deployment of this approach requires the use of some very specific tools, a brief overview of which is presented below.

Statistical Process Control (SPC) and Multivariate SPC (MSPC)

Sometimes the terms SPC and SQC are used interchangeably, thus creating confusion about their exact meaning. According to Woodall and Montgomery (69), Statistical Quality Control (SQC) is an area of industrial statistics, which includes acceptance sampling, Statistical Process Control (SPC), Design of Experiments (DoE) and capability analysis. The value of acceptance sampling after the 80s has declined under the strong influence of Deming, who considered it "too late costly and ineffective." On the contrary, the usefulness of DoE has been increasingly appreciated and will be discussed separately. Last, capability analysis is used to assess whether a stable process is capable of meeting the set specifications, and it is still considered an important technique.

Griffith (70) defined SPC as the application of basic statistics to control processes. The aim of SPC is to monitor production processes over time to detect changes in process performance (69). It is very useful in detecting unusual variability in the process due to special causes and identifying potentials for process improvements. It has been reported (16) that 95% of a workplace's problems could be solved by a selected number of quality tools often called the 'old seven,' 'first seven' or 'basic seven.' They were originally presented by Ishikawa (16) and are as follows: Pareto diagram, cause and effect diagram, check sheets, histograms, scatter diagrams, stratification and control charts. Often in the literature (71) the stratification tool (72) is replaced by the flowchart or the defect concentration diagram (11). These basic seven tools are considered indispensable for controlling processes and can be used for identification, prioritisation and communication of quality problems and to determine trends through the analysis of the data. According to Montgomery (11), the "magnificent seven" SPC problem-solving tools constitute a cohesive and practical framework for quality improvement. Ishikawa (16) believed that there are three levels of statistical tools. The basic seven are the introductory level, in which all employees should be trained; the intermediate level, which includes the use of distribution and sampling statistics, regression analysis, the basics of DoE etc.; and the advanced level, which includes methods such as DoE, multivariate and time series analysis.

One major SPC tool which is used extensively for process monitoring over time is the control chart (73). It can be employed in two phases. The first phase focuses on analyzing process data in order to understand the variation of a process over time and to evaluate its stability. Once the baseline is established, Phase II may start, which refers to process monitoring using on-line data to quickly detect shifts from the baseline. Montgomery (11) summarizes the fundamental uses of control charts as follows: managing of process variability, monitoring of the process, and estimation of product attributes or process parameters. When used properly, they increase productivity, provide diagnostic information and data for assessing process capability, prevent unnecessary process adjustments or, in other words, tampering with a stable system (74), and facilitate process control. Control is not defined as the complete absence of variability, but a state where all variation is predictable. Shewhart (18) originally stated in 1931 "we can predict that least within limits, how the phenomenon may be expected to vary in the future." A process is considered to be under statistical control when it is operating under the effect of common or chance causes only, and, thus, its performance is predictable. It represents a stable system of common causes, and its predictable variability is also called natural or inherent. This variability is unavoidable within a process. In the presence of assignable or special causes the process is considered out of control, and the control chart is the appropriate tool for differentiating these two types of variability.

The control charts, as introduced by Shewart, are based on the three-sigma control limits above and below the centre line balancing statistical and economic issues against false alarms, i.e. type I and type II errors. An out-of-control signal is given when a sample mean falls outside the control limits, and this is the basic criterion. However, additional criteria have been added to increase the sensitivity of Shewart control charts to small process shifts. Historically, the first four are called "AT&T instability rules" or "Western Electric Run tests" (75). Later on, Nelson (76) provided eight such rules for studying the control charts. These rules may increase their sensitivity, but at the same time they might also increase the number of false alarms, and this should be taken into consideration.

Two very effective alternatives to the traditional Shewhart control charts are the cumulative sum (CUSUM) and the exponentially weighted moving average (EWMA) control charts, which were introduced in the 1950s. While the Shewart charts are relatively insensitive in detecting shifts in the order of 1.5 sigma or less, these special charts

provide a solution when detection of small shifts is important. In contrast to the Shewart charts, they do not use the information only from the last plotted point, but they combine the information from several samples. Furthermore, EWMA can forecast the process mean, and, therefore, it can be used for real-time dynamic process control (69,77). The ability of the EWMA chart to predict values of time series has led to its application in automatic adaptive controllers (78). Both CUSUM and EWMA, which are also robust in the normality assumption in contrast to the Shewart charts, can be extended to solve multivariate quality control problems.

Process control charts are usually employed for monitoring one output of the process. However, this is not the case for many industrial applications, where quality is assessed through several related characteristics of the output, which is very common in process industries. Applying different control charts for every individual variable might be an obvious, but not the appropriate, solution, due to statistical reasons (11). Product quality is a multivariate, since it depends on achieving the desired values of all variables simultaneously. Thus, multivariate charts, where all studied variables are considered simultaneously, are necessary. The hotelling T^2 chart and the mutivariate type of the EWMA chart are considered as alternatives for dealing with such cases. However, their efficiency declines as the number of variables increases, and this is where the use of multivariate techniques like PCA and PLS emerged in order to overcome this restriction. (11).

Principal component analysis (PCA) is a multivariate method widely used for extracting relevant information from complex data sets by reducing their dimensionality and thus revealing the sometimes hidden, simplified underlying structures. Jackson (79) and Wold *et al.* (80) provided an overview of the PCA method. In brief, PCA transforms the original variables into a smaller number of uncorrelated variables called principal components, which are obtained as linear combinations of the original variables. The first principal component is determined in such a way as to represent the largest part of the variance of the data. The second component is computed under the constraint of being orthogonal to the first component and to have the largest possible variance. The rest of the components are computed likewise (81).

Partial least squares (PLS) is a method for constructing predictive models, when the variables are many and highly collinear. This prediction is achieved by extracting from the independent variables, also called predictors, a set of orthogonal factors called latent variables, which have the best predictive power (82,83). Overviews for PLS have been published by Wold (84) as well as Geladi and Kowalski (85). An interesting application of these techniques in a pharmaceutical, wet granulation and tableting example has been presented by Wehrlé and Stamm (86).

The potential of PCA and PLS to deal effectively with noisy and incomplete data and to give interpretable results has been used to monitor and control industrial processes, where large volumes of data are generated. The use of multivariate modelling in conjunction with SPC is called MSPC. MacGregor *et al.* (87–90) have extensively discussed the application of these methods for process monitoring and control of continuous and batch processes (91). A critical overview of batch process modeling and monitoring can be found in the literature (92,93).

The monitoring function of SPC to signal the presence of assignable causes is very useful, because after their removal the variability is reduced, and the process is in control. However, processes are usually drifting, and, thus, a variability of the output around its target is observed. Thus, there is a need to minimize this variability, and this is accomplished by Engineering Process Control (EPC) or Automatic Process Control (APC), stochastic control, or feedback/feed-forward control depending on the nature of the adjustments (11,94–96). The concept of EPC (11) is that proper adjustments can be made to the process in order to counterbalance what is driving the output off target, and, obviously, this requires a specific dynamic model linking inputs with outputs. In other words, EPC minimizes variability by transferring it from the output to a related input and controlled variable. Although SPC and EPC have been developed independently, they can be successfully integrated. They both have the same scope, i.e. reduction of variability, and they deliver this objective through two different but complementary ways. The combination of SPC and EPC for process monitoring is often called algorithmic SPC (97,98). Montgomery *et al.* (96) argued that perhaps SPC is a misnomer, since the main role of the statistical control chart is monitoring, while active control is carried out with EPC.

As mentioned above, statistical process control charts are a valuable means to ensure that a process is in control. However, just being in control is not the only requirement for a well-designed process. Processes also need to be capable, which means that when in control, they should also be able produce outputs meeting the set specifications. Capability analysis studies reveal if and how the voice of the process, i.e. its natural tolerance limits expressed in sigma, meets the voice of the customer, i.e. difference between the upper and the lower specification limit. The capability indices or ratios provide a simple and quantitative expression of process capability and have been used extensively by the industry (23). As pointed out by Goh (50), the capability studies and the control charts perform static and dynamic checks on the process, and when considered together may prevent the production of defective products and the deterioration of the process through its monitoring. However, they cannot be used as direct improvement tools,

since they passively analyse the output of the process. Therefore, there is a clear need to move from the passive approach, where quality is managed by process monitoring, to an active approach in which quality is improved through scientifically sound changes of the process inputs. This can be carried out with the experimental design methods.

DESIGN OF EXPERIMENTS (DoE)

Since most processes are too complex or poorly understood, there is a need to perform structured experiments in order to establish the causal relationship between their inputs and their outputs. The traditional method of changing one factor at a time (OFAT) has a lot of constraints, as it does not only require a large number of observations, but it also fails to reveal potential interactions between the factors, which is fundamental to understanding the system's behaviour (34). Design of Experiments introduced in the 1920s by R.A Fisher (99) is a much more efficient alternative strategy compared to the traditional OFAT approach (100). According to Montgomery (101), DoE is an experimental design approach in which the controlled input factors of the process are systemically varied to determine their effects on the output variables and to identify which are the most influential. It is extremely helpful in discovering the critical few factors that drive the process and their interactions, as well as to determine the values that these factors should have to ensure that the response is close to its target with the minimum variability possible. DoE has an established mathematical foundation behind the experimental procedures and, therefore, yields the maximum information for a given amount of data, resulting in experimental resource and time savings. It explores the operational space for all the selected inputs in relation to a specific response or responses of a process and allows the determination of the operational ranges that assure finished product quality (102).

DoE may be used for different applications extending from screening of factors to process characterization and optimization. Factorial designs either full or fractional and the Response Surface Methodology (RSM) are characteristic tools for this kind of application. It is also possible to simultaneously optimise multiple responses, which makes DoE a very useful and efficient technique in cases like pharmaceuticals, where quality is achieved through the optimization of several product characteristics (Multiple Response Optimization). Another useful application of DoE is when dealing with mixture components in which the response variable is a function of the relative proportion of each ingredient and not its absolute amount (mixture designs). This is quite common in the pharmaceutical industry in the area of formulation development (103).

Bhote (104) has characterized DoE as the key to the magic kingdom of quality, while Black *et al.* (105) have considered it as a strategic weapon to battle competitors worldwide by designing robust products, reducing time to market, improving quality and reliability and reducing life-cycle costs.

DoE is useful for several reasons (50): it has a proactive approach, it aims towards improvement through process understanding, and it is usually employed upstream in the development process. Therefore, DoE, while an off-line technique, is an active quality improvement tool for building quality into the product.

In addition to the DoE approach, there are other experimental design methods, like Shainin's experimental techniques for troubleshooting, Taguchi's methods for robust design, and the work of Box, Hunter and Hunter in applied experimental design and sequential experimentation strategies (50).

DoE and SPC tools have an obvious synergistic action when properly integrated for process understanding, improvement and monitoring; thus, their use in the QbD approach is very useful.

Risk Assessment

Risk assessment is a systematic process for the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (6). It is a means to identify and focus the efforts on the critical elements of a system, design, process or service. It involves three discreet steps: risk identification, risk analysis and risk evaluation. The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risks. Risk assessment methods have been used by industry for years; however, their use was supportive, focusing primarily on engineering or technical risks. As Chatterjee (106) suggested, Pharma industry should, instead of avoiding it, embrace risk and use risk assessment formally in all of its operations in order to identify and control potential risks. ICH Q8 and ICH Q9 mark a shift towards the use of risk assessment from the first stages of product development and across all Pharma operations to ensure high quality of medicinal products for the patients.

One of the commonly used methods for risk assessment is Failure Modes and Effects Analysis (FMEA). According to Stamatis (107), it is a methodology to evaluate a system, design, process or service for possible ways in which known or potential failures (problems, errors, risks, concerns) can occur. For each failure, an estimate is made regarding its occurrence, severity and detection in order to calculate the Risk Priority Number (RPN). An evaluation of the need to introduce controls or other measures that mitigate the risk of failure is then undertaken. The key point is to minimize

either the probability or the effect of failure. Other methods for identifying and quantifying risks include (6) Failure Mode, Effects and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), Hazard Analysis and Critical Control Points (HACCP), Hazard Operability Analysis (HAZOP), and Preliminary Hazard Analysis (PHA).

Knowledge Management and Continuous Improvement

It is well established that the pursuit of quality is a never-ending journey, and, thus, a culture of continuous improvement should always be maintained. According to Ishikawa (16), quality improvement (QI) can by achieved through two major approaches: continuous improvement, similar to the Japanese term *kaizen* in line with their concept of total quality, and full-scale breakthrough improvement, which Ishikawa called the Western approach.

Most of the well-known authors writing about quality, such as Deming, Juran and Feigenbaum, considered the continuous improvement culture as the major tenet of the holistic approach for quality. The well-known Plan, Do, Check or Study, Act (PDCA/PDSA) cycle embodies the central idea of the above-mentioned culture, while the change from check to study reflects the focus on studying instead of just checking the data.

Other more recent researchers define quality improvement as the company-wide process of focused and continuous incremental innovation or the culture of sustained improvement targeting the elimination of waste in all systems and processes of an organization (108). It is exactly this sustained quality improvement culture that supported the evolution of the quality principles as shown in Fig. 1.

On the other hand, newer concepts have emerged which have already affected not only a significant part of the academic and business sector, but also how management is or will be perceived in the future. One of the most important recent developments is the revolution about knowledge and learning in the digital economy and the inevitable impact in all types of organization. Quality improvement and innovation are both knowledge driven. T.A. Pearson (109) stated that the revolution is over and information won, while he proposed seven steps in a circle for building knowledge. It is characteristic that Deming's system for profound knowledge is placed at the center of his scheme.

It is now also clear that these developments gave rise to the knowledge-driven organizations, which are gradually replacing the product- and market-driven business entities (110). The era where demand exceeded supply and the target was to capture the rest of the market through increased production volumes and sophisticated marketing plans is now giving way to lean networked structures that create, capture and direct knowledge to the right people at the right time. This transition requires more flexible and agile environments, absolute focus on quality, i.e. meeting the real needs of the demanding customer, and delivering the right product at the right time without deviations from the agreed value. The response of the organizations should be immediate and of superior quality at the pull of the customer. Buckman (110) has identified three major elements for the transformation to a knowledge-driven organization: free flow and sharing of ideas, knowledge-driven products and services, and a knowledge-based strategy.

Today's organizational structures are reinventing the human dimension, and the term *workforce* is being replaced by the knowledgeable employee. The above could be linked to the 14 points of Deming to the Management and the Profound Knowledge concept developed several decades ago.

It should be realized that productivity is not increased by boosting production, since waste and inventory costs are also increased, but when three key factors are considered together: knowledge, leadership and siloless synergy (111). Knowledge has been identified as the key to reduce waste and the secret to more efficient plants. According to M.A. Lapre and L.N.Van Wassenhove (112), when conceptual (know why) and operational (know how) learning are both at a high level, they lead to science-based, operationally validated theories, and a plant-wide quality and productivity improvement can be realized. In contrast, when both are at a low level, this results in fire-fighting reactions. When the know-how is developed without any theoretical background, an art-based approach is evident. The latter might create some local improvements, which, however, can not be transferred to other production areas due to the lack of conceptual learning.

One significant practical application of the above-mentioned paradigm shift is the lean manufacturing concept. The lean plants or thinking production systems are able to produce high quality products at the pull of the customer in a 'just in time' approach, where the practical toolkit is used to bring problems to the surface to be solved by the thinking employee in a learning environment. The lean thinking or lean manufacturing (113) signaled the turning point from the mass production and economies of scale resulting in inflexible plants towards the economy of flow and elimination of all non-value-added activities or the so-called "seven wastes," such as overproduction, excessive inventory, making defectives, etc. (114).

Lean was considered the world-class manufacturing paradigm until the 1980s, when the fast and flexible concept evolved. This concept was officially introduced in 1991 and is also referred to as *agile manufacturing*. Agility is based on four key elements: delivering value to the customer, being ready for change, valuing human knowledge and skills, and forming virtual partnerships. The latter is the difference between the lean and the agile concept,

since in the latter the duration of partnerships is significantly shorter (115). According to Sanchez and Nagi (116), agility is a strategy focused on thriving in an unpredictable environment, where changes are continuous and unanticipated. It might be considered as the next paradigm for world-class manufacturing.

Lean and six-sigma are starting to attract the attention of the pharmaceutical industry. It was recently published that the lean concept was captured and implemented in four pharmaceutical manufacturing plants with impressive results regarding cost reduction and increased efficiency (117). Due to these clear benefits, it is believed that these practices will be adopted at a wider level by the pharmaceutical industry in the near future.

CONCLUSIONS

It is well established that pharmaceutical manufacturing is facing increasing pressure from two areas to improve its performance. One is emerging from competition and the well-established technological advancements from other types of industries, which are not yet widely adopted. The other originates from the regulatory initiatives on Quality by Design, which officially recognise the need to shift from the current state of manufacturing towards the future desired state, in order to address more efficiently the quality of medicinal products from the patient perspective.

The roadmap for this transition is well documented through the numerous research works and practical applications, a representative selection of which has been used in this article. The call is clear and has to do with a major culture change so that a new leadership will shift the product and market-driven pharmaceutical companies towards knowledge- and customer-centered organizations. The timely adoption of novel technologies throughout their system-based, networked and lean infrastructures will make them more agile in instigating changes which are continuous and sometimes unexpected. In light of the above, the relatively recent Guidances on Quality by Design should be viewed as triggers for the long organizational transformation journey required to meet the patient needs which might seem obvious, but are mostly implied and changing.

Who knows, perhaps the next definition of quality regardless of the industry type might be as follows: quality is a culture based on ethics, which assures that all the current knowledge has been used when delivering a product or service for the benefit of the society.

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