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CONTINUOUS IMPROVEMENT CONCEPTS AS A LINK BETWEEN QUALITY ASSURANCE AND IMPLEMENTATION OF CLEANER PRODUCTION – CASE STUDY IN THE GENERIC PHARMACEUTICAL INDUSTRY

Article Highlights

- CI as a relationship between QA and CP implementation in the generic pharmaceutial industry
- Application of Lean and Six Sigma tools for process improvement and link to other known concepts
- Evaluation of the production systems in terms of CI, considering both quality and efficiency

Abstract

The subject and the research objective presented in this article is establishing of the relationship between quality assurance and implementation of cleaner production in the generic pharmaceutical industry through the comprehensive concept of continuous improvement. This is mostly related to application of Lean and Six Sigma tools and techniques for process improvement and their link to other known concepts used in the industrial environment, especially manufacturing of generic pharmaceutical products from which two representative case studies were selected for comparative analysis, also considering relevant regulatory requirements in the field of quality management, as well as appropriate quality standards. Although the methodology discussed in this conceptual and practice oriented article is strongly related to chemical engineering, the focus is mainly on process industry, i.e., production systems, rather than any specific technological process itself. The scope of this research is an engineering approach to evaluation of the production systems in terms of continuous improvement concepts application, considering both quality aspects and efficiency of such systems.

Keywords: quality assurance, cleaner production, pharmaceutical industry, continuous improvement, lean, six sigma.

The present article is based on the application of specific continuous improvement techniques on relevant performance measures (PM) of different processes in the pharmaceutical industry and evaluation of their effectiveness in the actual industrial environment [1,2]. The processes that are studied in this work are related to design and operation of the equipment, as well as to the flow of the manufacturing process of the products under consideration, but also to quality systems relevant for production of pharmaceuticals. This implies optimization techniques of process design *versus* treatment processes (including techno-economic analysis) with the aim of introducing cleaner process technologies and how it relates to the improvement of the quality systems as well. Continuous improvement techniques also represent a part of chemical engineering, but in the sense of process industry, i.e. in the area of production systems, rather than any individual technological process. An original and novel approach is applied to the evaluation of industrial processes, as well as a new industrial engineering methodology and its application in practice is

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studied through the evaluation of the production systems, which are determined both by their capacities and quality aspects. The scope is therefore the processes in the generic pharmaceutical industry, which, as such, has certain specificities that have to be considered when evaluating the applicability of certain techniques in the area of continuous improvement.

Pharmaceutical industry is involved in development, production and marketing of drugs, *i.e.*, pharmaceutical products approved by relevant regulatory authorities. Pharmaceutical companies can have their own research and development – originators, *i.e.*, innovators, or produce generic drugs – products bioequivalent to the innovator's, *i.e.*, comprising the same medicinal or therapeutic substances as the original drug. Pharmaceutical companies based on their own development made a significant progress in treatment of numerous diseases, but increasing healthcare costs over time also resulted in the increased use of generic drugs with certain advantages over more expensive original drugs, especially among the poorer population of patients. Because of this, generic pharmaceutical production represents a significant portion of the world pharmaceutical industry. Either based on its own development or generic, pharmaceutical industry is regulated through numerous laws and regulations in the area of patenting, testing and ensuring safety and efficiency of drugs, *i.e.*, product release to the market.

The aim of this work is to evaluate the relationship between process performance measurement with key indicators of success on the company level and the concept of introducing cleaner production principles in the generic pharmaceutical industry, linked to the continuous improvement programs.

THEORETICAL PART

It is a well known fact that pharmaceutical production is one of the most regulated industrial sectors and that quality is the key factor that determines each manufacturing system, including product characteristics, its appearance, duration, maintenance, but also its supply and relevant documentation. For the purpose of achieving sustainable success, the organizations regularly measure, analyse and review their performance, including evaluating the progress in achieving planned results compared to their mission, vision, policies, strategy and goals on all levels and in all relevant processes and functions in the organization. Measurement and process analysis is used to track this progress, gather and have all the necessary information available to evaluate performance and effectively make decisions. Selection of the appropriate key performance indicators, as well as measurement methodologies, represents a critical factor for the success of measurement and analysis procedures.

In the new philosophy of sustainability, the concept of sustainable development is replaced with the term sustainable success, as a result of the organization's ability to achieve and maintain long-term goals, and this is the main novelty in revised standard ISO 9004: 2009 [3] in relation to the second revision of this standard [4]. ISO 9001 [5] specifies the requirements for the quality management system and is focused on its effectiveness in complying with customer requirements. ISO 9004 gives additional guidance for the organizations willing to move further than these requirements, to solving the needs and expectations of all interested parties and their satisfaction through systematic and continuous performance improvement. Therefore, it represents a powerful tool for the management, and the sustainable success of the organization is developed through its capability to satisfy needs and expectations imposed by its customers and other interested parties in a balanced way and over a long period of time. Self-assessment is used to identify areas for improvement and innovation, establish priorities and develop action plans aimed at sustainable success. The results of the organization's evaluation according to ISO 9004 may represent a valuable input for management review as required by ISO 9001 (*i.e.*, for information review from monitoring, measurement and analysis, as stipulated in ISO 9004:2009), but this self-assessment process also has a certain potential to be a learning tool enabling the improved involvement of interested parties whose needs and expectations have to be properly understood, as the key element of the organization's maturity model.

Cleaner production and eco-efficiency are part of the consideration in the area of the environment, as prescribed by the social responsibility standard. These are the strategies for satisfaction of human needs through more efficient utilization of resources and producing less pollution and waste. Significant focus is to introduce the improvements at the source instead at the end of process or activity. Cleaner and safer production, as well as eco-efficiency approaches include also the improvement of the sustainable practice, introducing new technologies or processes with lower consumption of material and energy (*i.e.*, utilization of its renewable resources) and rationalization of water consumption. Cleaner production assumes elimination or safe management of toxic and hazard-

ous materials/wastes, as well as improvement of the products and services projects. Cleaner production in general represents a contemporary approach in preventing the creation of pollution that provided the greatest contributions in the production sector, especially in industry [6].

Six Sigma approach to continuous improvement uses the methodology known as DMAIC (Define, Measure, Analyze, Improve, Control) for process improvement from beginning to end [7]. In each of these phases, appropriate tools are being used, such as project plan, SIPOC (Supplier, Input, Process, Output, Customer), process mapping and different team management techniques in the define phase, measurement system analysis, histogram and Pareto in measure, FMEA (Failure Mode and Effects Analysis), "5 whys" and fishbone diagram for cause-and-effect analysis, statistic process control and control charts in the control phase of the implemented improvements.

According to well known statistical principles, sigma represents a Greek letter for standard deviation showing how much the measured results are distant from the average of the observed set of data, *i.e.*, representing a measure of process variability and its capability to work without errors and as little variation as possible. Measures are necessary in order to determine whether the process of interest is stable and predictable, as well as how much variation is present [8]. Six Sigma means that the interval between both upper and lower limit of the process specification and the average of the results obtained from that actual process is 6 standard deviations. This number of standard deviations is inversely proportional to the probability of defects and in fact illustrates how much of the obtained results is within the interval required by the customer, i.e. increasing the sigma level of the process decreases the cost and increases productivity and customer satisfaction. In order to state that a process is "sigma" it is not allowed to have more than 3.4 defects per million opportunities [9], therefore six sigma virtually represents a measure of quality practically aiming for perfection. ISO/TR 10017:2003 also provides guidance on the selection of appropriate statistical techniques that may be useful to an organization in developing, implementing, maintaining and improving a quality management system in compliance with ISO 9001 [10].

Lean, on the other hand, is a concept originating from Toyota in the 1950s and representing a common sense and practical approach to solving problems with the focus on identifying and eliminating waste from the process. Over the years, Toyota started a global transformation in almost all industry sectors in accordance with Lean philosophy in the area of manufacturing and supply chain [11]. There are seven common forms of waste, namely: transport, inventory, movement, waiting, over-production, over-processing and defects, and one of the tools introduced by the Lean methodology is Kaizen (Ky = change and Zen = = for the better, generally being translated as continuous improvement through solving problems). Kaizen is a quick, intensive look at the process with the aim of improvement. It gathers customers, suppliers, support and people performing the work, where the latter is key for its success. The actual process is observed and waste identified and eliminated through establishing a new process but as a continuous effort rather than reaching perfection in one step. Production system established in Toyota is the starting basis for numerous literature sources in this field, including *The Machine That Changed the World: The Story of Lean Production* [12] and *Lean Thinking* [13].

The international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) in its guidance Q10 [14] describes one comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization (ISO) quality concepts, includes applicable good manufacturing practice (GMP) regulations, and complements ICH "Q8 Pharmaceutical Development" and ICH "Q9 Quality Risk Management." ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

In this work, the selected criteria used to determine the existence of either Lean or Six Sigma approach (or both) in the case studies subject to evaluation are as follows: 1) data based approach/performance measurement, 2) link to the customer, 3) proactive thinking and 4) tools and techniques. Additionally, the link between the processes subject to relevant case studies (quality assurance – QA and cleaner production – CP) was analyzed against relevant regulatory requirements and quality standards.

CASE STUDY

Starting hypotheses are based on the importance of measurement as the key element to control,

manage and improve processes on one side and the link of continuous improvement to the cleaner production concept in the industrial environment on the other. Performance measurement represents the basis of most continuous improvement programs, enabling for example the implementation of cleaner production step by step, using appropriate tools and techniques. This is especially true for generic pharmaceutical industry where it is necessary to change technological procedures in a highly regulated environment in contrast to minimizing harmful effects of the production processes in the end-of-pipe approach.

Therefore, the scope of this study is to evaluate the following:

- Performance measurement system represents the comparison of the current values with the predefined objectives and enables feedback to the participants in the process - this approach should result in the improvement of the quality management system and continual adjusting of the performance measures.
- Implementation of the continuous improvement program based on process performance measurement leads to decreased costs related to different forms of waste, *i.e.*, redundant engagement of resources.
- Efficient elimination of waste from the processes with positive effects on quality, environment, working conditions and social responsibility at the same time, can be accomplished through a unique approach of the continuous improvement program implementation, introducing step by step improvements in individual areas.

This evaluation is performed using the examples of quality assurance processes [1] as the case study CS I, and dealing with volatile organic compounds (VOCs) emissions, as one of the challenges for the implementation of cleaner production in the generic pharmaceutical industry [2], as the case study CS II.

Description of the analyzed case studies

CS I in the area of quality assurance was aimed to evaluate the implementation of the modern approach based on measures and key performance indicators in a pharmaceutical company using the example of the delivery time improvement through decreasing the number of deviations and time spent on unnecessary investigations. Problems subject to the analysis were identified in both cases based on relevant information and data available in the industrial information system related to actual processes, and appropriate corrective actions and suggested improvements were implemented through the described improvement projects. Results were discussed relative to the previously established objectives: in the area of quality assurance, significant decrease of total number of deviations was shown – more than 50% [1].

On the other hand, as CS II for introducing the cleaner production principles into the processes within the generic pharmaceutical industry, the case of tablets coating was selected, as one of the most common and widely used operation in the pharmaceutical production in general. The conclusion was made that the option of preventing pollution through modifying the formulation has a significant advantage both considering financial benefits and minimization of waste, i.e. negative impact on the environment [2].

Data based approach/Performance measurement

In CS I, methods used for gathering the information related to key performance indicators (KPI) are selected as feasible and appropriate for the organization, which is also one of the requirements in ISO 9004:2009 (Figure 1). On the other hand, the KPI is

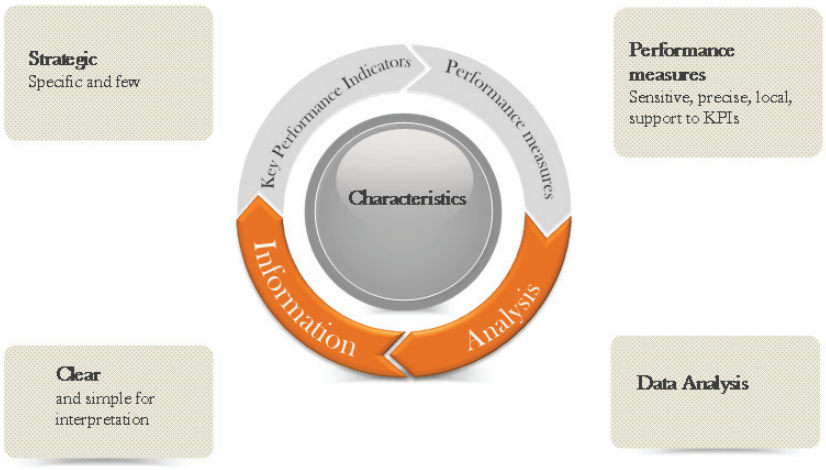

Figure 1. Main characteristics of the key indicators, performance measures and data analysis performed.

selected to enable its quantification and make feasible to the organization to set measurable goals, identify, monitor and predict trends and implement corrective, preventive and improvement measures, as needed. It is important to ensure that measurable and reliable information are available for the implementation of these corrective actions when the performance is not in compliance with the previously established goals.

As efficient utilization of resources is also one of the requirements that need to be assured by the management system, it is shown in the CS II that the processes are established to monitor and optimize these resources in order to ensure their effective and efficient use. Therefore, the organization continually measures their current utilization to identify opportunities for the improvement in this area. In addition, the environmental impact was measured as part of continual monitoring to enable the organization to identify and implement the appropriate risk management in this area.

Link to the customer

In the CS I the selected KPI is decomposed as a performance indicator in relevant functions and levels in the organization to support reaching the higher level objectives in line with the strategy and corporate policies (Figure 2).

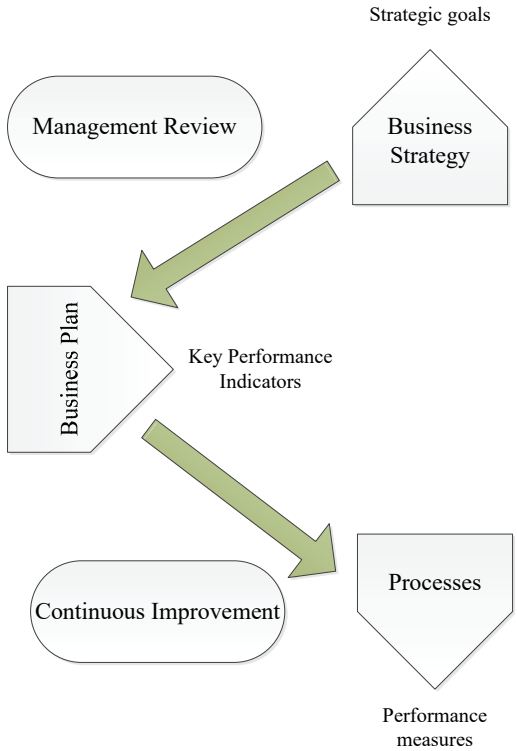

Figure 2. Link between strategic goals, key indicators and performance measures.

Organization performance measurement thus represents an important source of data for a systematic approach to evaluation of the available information to assure that this information serves as a basis for making important decisions. Improvement, innovations and learning can be applied on products, processes and technology, as well as on organizational structures, management systems, infrastructure and work environment and the basis for this is the capability of the organization to draw conclusions based on relevant data analysis. One of the key benefits of continuous improvement, besides improving performance through enhanced capability of the organization and harmonizing the improvement activity at all levels, in accordance with its strategic orientation, is the adaptability, *i.e.*, flexibility to respond fast enough to opportunities, mostly in terms of increased competitiveness on the market.

Security management within the supply chain for which the KPI is selected for evaluation in CS I is related to numerous other business aspects, and relevant requirements covering these management systems are defined in ISO 28001:2007 [15]. According to this standard, the supply chain represents the interlinked ensemble of resources and processes beginning with the source of raw materials, through product and/or services supplied to the end user by means of different kinds of transport. The system of supply chain managements in the CS I is also subject to continuous improvement.

Cleaner production as a concept evaluated in CS II can be indirectly linked to the population of pharmaceutical industry customers through sustainable development taking care of limited environmental capacity to receive a specific quantity of waste, mostly related to industrial pollution. The relationship between the elements of procurement, production and the consumers in a broader sense is shown implying the need to develop preventive activities through the product life cycle. This is additionally supported by the fact that cleaner production represents an application of the comprehensive preventive strategy of environmental protection on the production processes, products and services with the aim to increase overall efficiency and decrease health and environmental risks (UNEP), meaning preservation of resources, water and energy, reduced application of toxic and hazardous raw materials and reduced quantities and toxicity of all emissions and wastes at the source of the production process instead of the End-of-Pipe technologies (Figure 3).

Cleaner production does require significant changes in the organization and its processes. This

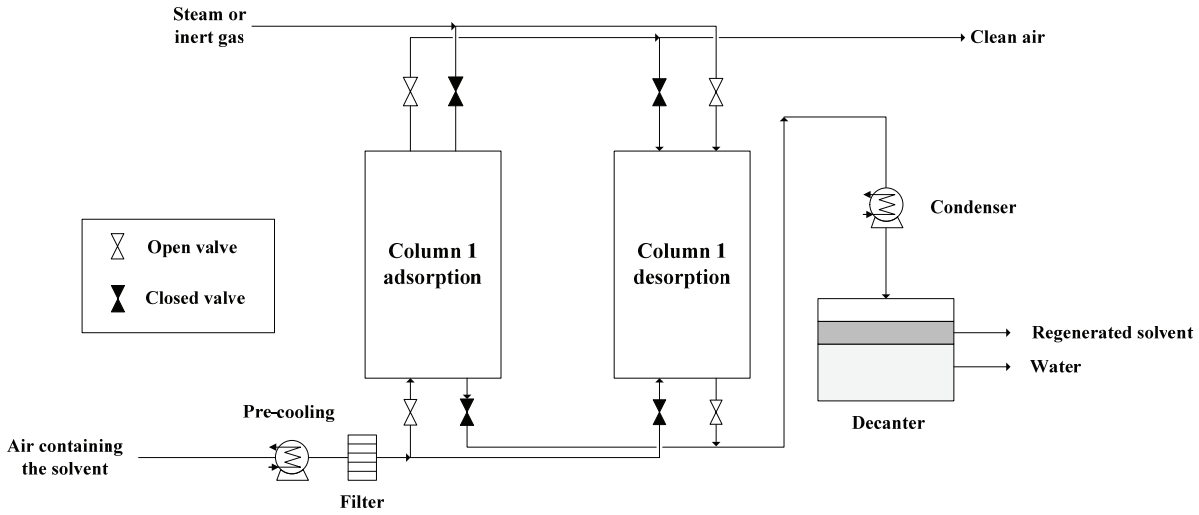

Figure 3. Example of EOP - a typical adsorption process for VOCs [16].

can be accomplished through an approach that can bring benefits to all interested parties, which is also shown based on the techno-economic analysis performed as part of CS II.

Proactive thinking

Processes and their relationships, as shown in CS I, are regularly reviewed and appropriate actions are taken for their improvement. In the course of planning and management of these processes, the organization's environment was considered and analyzed, mostly taking into account relevant regulatory and other requirements. The planning process according CS I considers the established needs of the organization to develop or apply new process characteristics as an added value, which at the same time represents one of the requirements of ISO 9004:2009.

In CS II, the focus is on process optimization and new technologies. When it comes to the infrastructure which is planned, enabled and managed by the organization in an efficient and effective manner, appropriate attention is also given to safety and protection, the elements of this infrastructure linked to production processes, as well as its impact on the working environment, overall efficiency, costs and capacities. At the same time, working environment is evaluated in accordance with applicable laws and other regulations in the field of environmental, health and safety management. Therefore, technological opportunities were considered in CS II to improve organization performance in different areas, including product realization and interaction with interested parties. It is shown that the organization is also considering the integration of the environmental aspects in the design and product development, as well as developing the specific processes to minimize the identified risk in the field of environmental management. Furthermore, cleaner production is by its definition a proactive approach to dealing with the environmental impact of the processes in all industries. Using prevention in formulating environmental protection policy is also required according to ISO 140001 [17] and cleaner production completely supports this concept complying with the organization's practices for environmental management systems in achieving the common objectives to continually implement the improvements. Živković *et al.* have done a case study for the Oil Refinery Belgrade that confirmed an improvement of environmental performances using the ISO 14001 standard [18].

Tools and techniques

Pareto diagrams were used in CS I as a tool to focus attention to problems offering the greatest potential for improvement. This technique is based on the rule that 20% of causes lead to 80% of problems (Pareto principle). Fishbone diagram or root cause analysis was also applied in this study (CS 1) representing a visual description of individual contributions to a certain problem. The fish head represents a problem to be solved while the bones serve to picture the root causes classified in 4–6 main categories: materials, methods, people, machines, the environment and measurement. Additional categories or further classifications within individual categories are also possible depending on their importance.

Suitable working environment, as a combination of human and physical factors, assumes also maximum efficiency and minimization of waste, which is one of the key principles of Lean manufacturing and the basis of the CS II at the same time. Furthermore, cleaner production focuses on the root causes of

problems related to the environment and not the consequences, which is one of the main goals in the six sigma analyze phase of the improvement process.

RESULTS AND DISCUSSION

Results of the two case studies analysis against pre-defined criteria are summarized in Table 1.

Additionally linked to CI through regulations and quality standards (a-e are referred in Table 1):

a. ISO 9004 requirements;
b. ICH Q10 and GMP requirements;
c. System of ecological management;
d. ISO 140001 focus on prevention;
e. Similar to PDCA in ISO 9001.

Linking the objectives in the field of environmental protection with improved productivity, material savings and decreased cost of handling and waste management, cleaner production is imposed as an inseparable part of the overall strategy to improve performances and increase total efficiency. Environmental protection aspects may be regarded as an important motivation factor to come to innovative solutions leading to both safety increase and significant financial benefits. As a result, a natural link is developed between the environmental goals and improvement projects initiated to increase productivity, achieve better yields, implement savings in materials and decrease the cost of waste management. Therefore, cleaner production becomes an important element of the comprehensive strategy of performance improvement and efficiency increase through the application of production concepts in accordance with Lean principles.

Based on the studied facts, as well as numerous literature findings in this area, but also with regards to practical experience in management of the quality assurance processes and pharmaceutical production in general, it is obvious that the continuous improvement programs can be considered as the link between establishing sustainable process performance measurement systems and implementation of cleaner production in the pharmaceutical industry (Figure 4).

Requirements for the Pharmaceutical Quality System are stipulated in ICH Q10 [14] and related to quality assurance processes as described in Good Manufacturing Practice. Performance measures eva-

Table 1. Comparative analysis against the suggested Continuous Improvement Criteria

Continuous Improvement (CI) Criteria	CS I related to QA processes	CS II related to CP
Data based approach/	data gathered to support the selected KPI[a]	Monitoring and optimization of resources
Performance measurement	PMs established in relevant functions[b]	Measuring the environmental impact
Customer orientation	KPI and PMs link to strategy to achieve flexibility in terms of market requirements through KPI selection for supply chain management	Indirectly through sustainable development[c] Techno-economic analysis
Proactive thinking	Regular review of processes and measures for their improvement	Focus on optimization and new technologies Evaluation against applicable laws and regulations Integration of environmental aspects in design and Product development[d]
Tools and techniques	Pareto Fishbone	Lean manufacturing Kaizen philosophy[e]

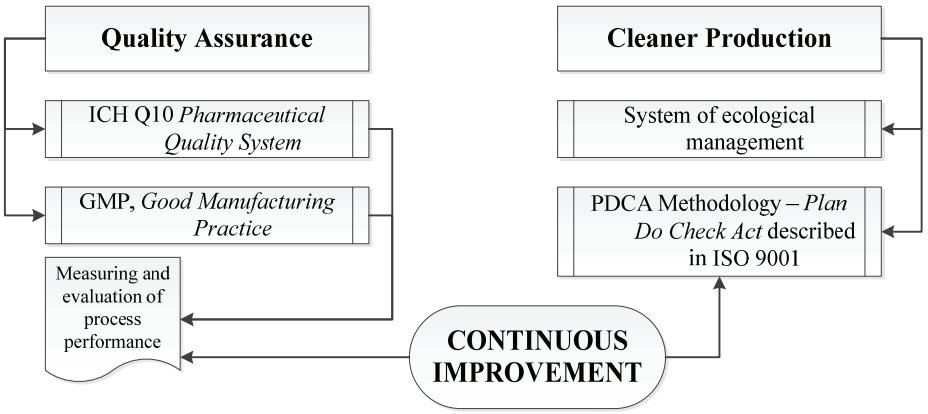

Figure 4. Continuous improvements as the link between quality assurance and cleaner production principles.

luation in terms of quality management processes is one of the key activities required for achieving the continuous improvement as one of the most important requirements of the Pharmaceutical Quality System given in ICH Q10. At the same time, system of ecological management, as one of the cleaner production elements, is also an instrument to recognize and solve environmental problems based on the continuous improvement concepts. Implementation of the Q10 model should facilitate continual improvement, in order to identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill a pharmaceutical manufacturer's own quality needs consistently. Quality risk management represents a logical path adopted by an organization that has successfully implemented the basics required by ISO 9001, as it provides broader focus on the quality management system through a wider model based on processes. It relates to needs and expectations of all interested parties and gives instructions for systematic and continual improvement of overall performance of an organization. Additionally, ISO 9004 also comprises broader requirements for management of the resources and their efficient use, which again brings performance measurement within the quality system in relation to cleaner production principles through the concept of continuous improvement (Figure 5).

It is clear that in both case studies the focus was on the contemporary requirements of the ICH Q10

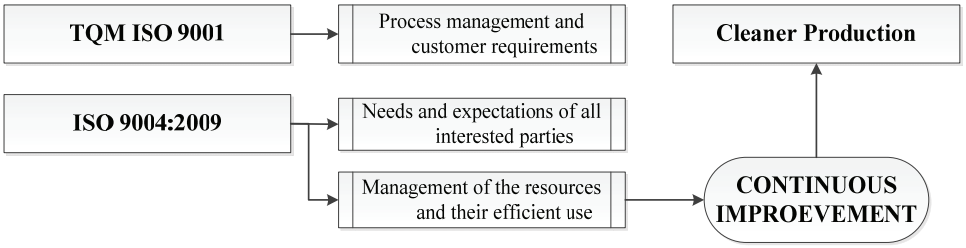

Figure 5. The link between performance measurement and cleaner production through the concept of CI.

can be useful for identifying and prioritizing areas for continual improvement.

The results of the performed study may also be summarized are follows:

- single methodology for improvement of quality management and industrial processes through continual monitoring and control of relevant performance measures;
- correlation between different regulatory requirements for pharmaceutical industry to enable compliance through implementation of a single concept of continuous improvement;
- dissemination of continuous improvement philosophy and knowledge in the area of integrated environmental and quality management, as well as safety, all in accordance with the main principles and key aspects of social responsibility.

Performance measurement plays the key role in the area of quality management, providing insight in parts of the process where change and improvement is required, necessary feedback as the basis for further improvements, as well as relevant information for analysis and evaluation of the achieved performance. When it comes to models based on Total Quality Management (TQM), process management and customer orientation are regarded as the key factors for implementation. On the other hand, new ISO 9004 related to establishing the process performance indicators in critical areas within the Pharmaceutical Quality System and implementation of the continuous improvement concept in general, leading to evaluation of the overall organization performance through ISO 9004 and enhanced model based on processes, as well as taking into consideration the needs and expectations of all interested parties, which defines the CI as a common term both for quality management and cleaner production principles.

CONCLUSION

Measures and KPIs represent an important element of the CI concept, which on the other hand plays the key role in the modern Quality Management System (QMS) of the pharmaceutical company. The appropriate application of the process performance measurement system actually means measuring the current values of the specific parameters against the objectives and providing the feedback to relevant participants in the process. This approach should lead to the continuous improvement of the QMS, as well as performance measures in various processes, including sustainable environmental protection.

Applying the appropriate Lean and Six Sigma tools and techniques, further significant problems

categories can be identified to be gradually solved leading to completely eliminating, *e.g.*, an entire class of deviations or environmental impacts when it comes to harmful emissions for example. Additionally, links and precise correlations can be determined between such performance measures managed locally and higher level objectives and the analysis can be expanded to other processes supporting these objectives. In this regard, the approach and concept of application of appropriate tools and analysis methods shown and developed in this work may be readily used in all similar improvement projects through different areas of the quality system and generic pharmaceutical production.

Acknowledgements

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NAUČNI RAD

KONCEPTI KONTINUIRANOG UNAPREĐENJA KAO VEZA IZMEĐU OBEZBEĐENJA KVALITETA I UVOĐENJA ČISTIJE PROIZVODNJE – STUDIJA SLUČAJA U GENERIČKOJ FARMACEUTSKOJ INDUSTRIJI

Predmet i cilj istraživanja koje je predstavljeno u ovom radu jeste uspostavljanje veze između obezbeđenja kvaliteta i uvođenja čistije proizvodnje u generičkoj farmaceutskoj industriji kroz sveobuhvatni koncept kontinuiranog unapređenja. Ovo se u najvećoj meri odnosi na primenu "lean" i "šest sigma" alata i tehnika za unapređenje procesa i njihovu povezanost sa drugim poznatim konceptima koji se koriste u industrijskom okruženju, a posebno proizvodnji generičkih farmaceutskih proizvoda, gde su za potrebe komparativne analize odabrane dve reprezentativne studije slučaja, uzimajući u obzir i relevantne regulatorne zahteve u oblasti menadžmenta kvalitetom, kao i odgovarajuće standarde kvaliteta. Iako je metodologija razmatrana u ovoj konceptualnoj i praktičnoj studiji usko povezana sa hemijskim inženjerstvom, akcenat je u najvećoj meri stavljen na procesnu industriju, odnosno proizvodne sisteme, pre nego na pojedinačne tehnološke procese. U tom smislu, predmet ovog istraživanja jeste inženjerski pristup evaluaciji proizvodnih sistema u pogledu primene koncepta kontinuiranog unapređenja, uzimajući u obzir kako aspekte kvaliteta, tako i efikasnost tih sistema.

Ključne reči: obezbeđenje kvaliteta, čistija proizvodnja, farmaceutska industrija, kontinuirano unapređenje, "lean", "šest sigma".