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Improvement of the Supply Chain in the Pharmaceutical Industry using a Lean approach

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Abstract

Lean is a philosophy which has proven its added value in many sectors. Although this philosophy is based on process simplification and wastes elimination, it is however complex to implement.

Poor culture for continuous improvement may be an obstacle for Lean implementation as well as the systemic barriers in some industries. The Pharmaceutical Industry seems to be among these industries where difficulties can be encountered during Lean deployment. While outsourcing which is a practice well-established in the Pharmaceutical Industry would make Lean deployment throughout the Supply Chain harder to perform and maintain, the regulatory framework would create somewhat inflexible environment where a core concept of Lean like Just in Time is difficult to put in place.

Nevertheless, there are cases of successfully implemented Lean project in the Pharma sector which demonstrate that Lean philosophy is not incompatible with the Pharmaceutical Industry.

Considerations like quick return on investment may prevent the interest for this philosophy. Lean initiative must not be hampered because it does not represent the best short-term solution in terms of cost. Lean is a strategy whose the benefit can be seen only by the organization who begins this endless journey.

Résumé

Le Lean est une philosophie qui a fait ses preuves dans de nombreux secteurs. Bien que cette philosophie soit basée sur la simplification des processus et l'élimination de tout ce qui n'est pas nécessaire dans un procédé, elle est complexe à mettre en œuvre.

Une culture faiblement engagée pour l'amélioration continue ainsi que les barrières systémiques dans certaines industries peuvent être des obstacles à sa mise en œuvre L'industrie pharmaceutique semble faire partie de ces industries où des difficultés peuvent être rencontrées lors du déploiement du Lean. Alors que l'externalisation, qui est une pratique bien établie dans l'industrie pharmaceutique, rendrait le déploiement Lean tout au long de la chaîne d'approvisionnement plus difficile à réaliser et à maintenir, le cadre réglementaire créerait un environnement quelque peu rigide où un concept de base du Lean comme le 'juste à temps' est difficile à mettre en place.

Il existe cependant des cas de projets Lean misent en œuvre avec succès dans le secteur pharmaceutique qui démontrent que la philosophie Lean n'est pas incompatible avec cette industrie.

Des considérations telles que le retour sur investissement rapide peuvent empêcher l'intérêt pour cette philosophie. L'initiative Lean ne doit pas être entravée parce qu'elle ne représente pas la meilleure solution à court terme en termes de coût. Le Lean est une stratégie dont l'avantage ne peut être vu que par l'organisation qui commence ce voyage sans fin.

Preface

More than ten years after starting my professional career, I made the choice to take up studies again with a Master at UCLouvain in the sciences of management.

So first of all, my thoughts are with my wife and my two little daughters, to whom I have devoted less time over the past year.

I thank also Professor Jean-Sébastien Tancrez for his advices regarding the direction to take for the analysis specially when I encountered difficulties to collect data on the field.

Regarding the theme of this Master's thesis, it is due to my interest for the Supply Chain activities in general and in initiatives aimed at simplifying things. I have been working in the Pharmaceutical Industry since 2011 with several roles in Quality Assurance and in Production departments. In some instances, I found the processes I was in charge of very complicated. So, in this Master's thesis, I tried to reveal the reasons that make the processes complex in the Pharmaceutical Industry and how Lean can simplify them.

I wish you a pleasant and insightful reading.

Engin Deniz

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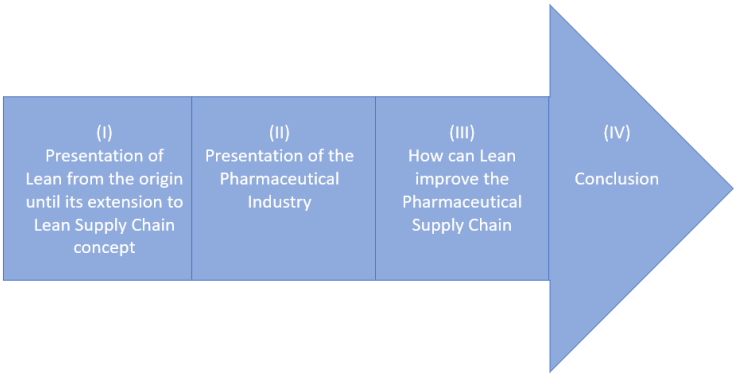
1. Introduction

Lean philosophy gained worldwide popularity when western authors started writing books and articles on it to explain how this approach helped the Japanese firm Toyota to develop an edge in the automotive industry. Since then, Lean has been implemented in many other industries. In this Master's thesis, the opportunities for improvement in the Pharmaceutical Industry through Lean approach will be presented. The plan of analysis can be described as such:



The presentation of Lean (I) and the Pharmaceutical Industry (II) will be made based on a literature review and also on the regulatory framework of the Pharmaceutical Industry.

The use of practical cases presented in scientific articles will show how Lean can improve the Pharmaceutical Supply Chain (III). A joint analysis of some regulatory requirements and Lean goals will help to identify as well some potential barriers for the implementation of Lean.

Finally, a conclusion (IV) will be provided with some recommendations.

The manufacturing processes in the Pharmaceutical Industry are very heterogeneous due to the drugs' dosage forms for example. In this Master's thesis, one general process for the manufacturing of drugs will be presented to show the complexity of this industry. It was initially also planned to interview professionals managing Supply Chain activities in Pharmaceutical companies based in Belgium in order to collect their experiences regarding the issues they encounter in the Pharmaceutical Supply Chain as well as to discuss about the use of Lean. These feedbacks would have been compared to the theoretical conclusion of this thesis to evaluate its consistency. However, due to many refusals mainly for confidentiality reasons, it was not possible to conduct these interviews. This may represent a limit in the analysis performed in the context of this Master's thesis.

2. Lean philosophy

2.1. Introduction

In this Part 2, Lean will be presented through its major concepts in order to allow the reader to quickly assimilate the idea behind this methodology. From its origin to its application in the field of Supply Chain passing also through its rapprochement with the concept of Six Sigma, an overview of this system of thoughts will be given.

The literature about Lean is plentiful. Hence, alternative approaches could have been used to present the Lean methodology. The following point must be clarified as well: the goal of this section is not to present all the existing tools and techniques used and developed by the Lean practitioners.

2.2. Origin of Lean

The book *"The Machine that Changed the World"* written by Womack, Jones & Ross (as cited in Gao & Low, 2014, p. 28-29*)* was the first book to focus attention on the term Lean, in which the authors emphasized the differences between Toyota plants and the Motor industry in the United States. According to them, the production philosophy of Toyota was superior to all the other systems because it produced high quality products with less investment, less effort from the workforce and less inventory (Gao & Low, 2014). So it can be assumed that Lean or Lean Management (LM) takes its roots from manufacturing best-practices that were implemented in the Toyota Motor Corporation such as Total Quality Management (TQM) or Just in Time (JIT) (Oleghe & Salonitis, 2018).

2.3. The Toyota Production System

The Toyota Production System (TPS) through its composing elements can be considered as a full reference for consistent Lean deployment strategy. TPS can be drawn as a house composed of five elements (Liker, 2020). These elements are described in the next sub-sections.

2.3.1. In-Station Quality

The right pillar called “In-Station Quality” (or Jidoka in Japanese) refers to the need of paying attention to the problems. In other words, a defect cannot escape the station (Liker, 2020). The idea behind this is to build quality in the process by stopping production line or process once there is problem being detected.

Monden (as cited in Gao & Low, 2014, p. 82) detailed two approaches used to stop and fix production when issues or abnormalities occur:

(i) By relying on human judgment: the workers are given the responsibility to stop the line in situations where the operations cannot be performed in accordance with the standard operations routine.

(ii) By the use of automatic devices: instruments detecting abnormalities stop the line and a signal is given to notify the workers (it can be a camera monitoring the presence of a defect associated with an alarm that will then give the signal).

2.3.2. Just in Time

The left pillar is “Just in Time” (JIT). The term JIT originated from a scheme called Kanban but it would be too simple to reduce JIT to a product call system using card or any suitable signal. So two important principles are going to be used in order to understand what JIT means:

(i) The pull principle: pull system is one of the Lean manufacturing principles used to reduce waste in a process. In pull system, components used in the process are only replaced once they have been consumed. Push system is the opposite principle in which as many products as possible are produced to be sold via marketing activities. The goal of pull system is to avoid overproduction of goods or services to deliver. In other words, the next step in the chain “pulls” value through the process.

(ii) Flow principle: value must be added in an uninterrupted flow throughout the production process. The advantages of a continuous flow are stability, balance and continuity. There is no or very little time wasted between steps which maximizes the process capabilities. It is an ideal process state (Helmold, 2020).

2.3.3. Operational Stability

In order to maintain both pillars of this house, stability is needed. In the Toyota Production System, this stability exists through the operational stability. For instance, standardized work and reliable suppliers contribute to the robustness of this stability. In standard work, teams create the standards that define the work. Any improvement of the process is done from this standard work that serves as a baseline. Suppliers partnerships is another crucial element for the success of a production system. Integrating suppliers as partners into the production system would reduce setup times, inventories or defects because they undertake to deliver services or parts to the manufacturer in a timely manner (Nicholas, 2010).

2.3.4. Culture

The culture for continuous improvement is at the heart of the Lean System. The Japanese term "Kaizen" is used as synonym of continuous improvement. The main goal of kaizen is to continuously improve processes, products and working areas. This can be done by integrating the people of the affected areas. The PDCA cycle also known as the Deming circle is a tool in the context of kaizen. It is an iterative management method in four steps:

(i) Plan: Analysis of the current situation and definition of the improvement plan.
(ii) Do: Implementation of the defined solutions.
(iii) Check: Evaluation of the results.
(iv) Act: Standardization of the best solution or re-adjustment.

With standardization, the process cannot return to the old state and when it is secured, it is ready for the next improvement (see Figure 2.1). Another important aspect of Kaizen is the time and the effort dedicated to the improvement. Kaizen is not innovation but rather a dynamic state that is conducive to small improvements without requiring high investment except the involvement of the people (see Figure 2.2).

2.3.5. Waste elimination

This last component of the TPS house is the final objective of the Lean approach but an organization needs to be at an advanced stage regarding the four elements of the TPS house described previously (JIT, Jidoka, Operational Stability, Kaizen Culture) before to be a

champion of waste elimination. Any process in an organization that is not adding value is considered as waste and the goal of Lean is to eliminate wastes (Nicholas, 2010).

The adding value or non-adding value processes must be identified through a customer perspective. Ohno' seven wastes is a simple concept that will be used for identifying the wastes that Lean tries to eliminate in order to improve the chain of values. This seven wastes approach can be applied to many services even though these wastes categories were originally for manufacturing (Bicheno & Holweg, 2009).

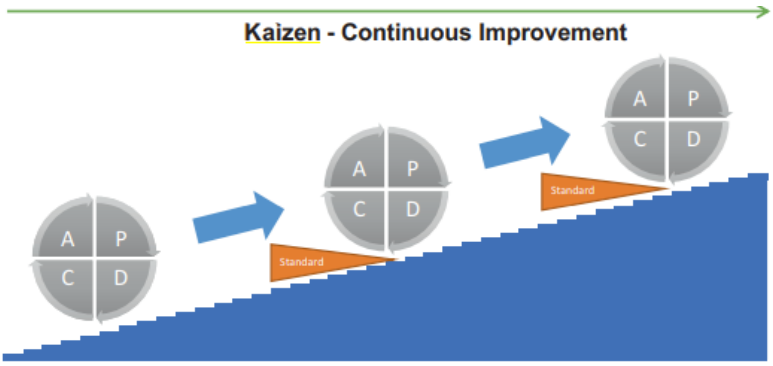


Figure 2.1 - Kaizen cycle (PDCA) (adapted with permission from Helmold, 2020, p.27).

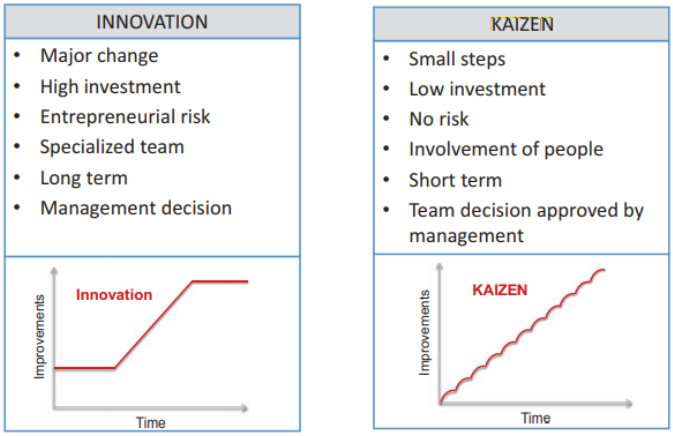


Figure 2.2 - Innovation vs Kaizen (adapted with permission from Helmold, 2020, p.27).

2.3.5.1. The waste of overproduction

While the ideal situation should be to make exactly what is required in terms of quantities, on time and with high quality, overproduction is making too much and too early. A process should not encourage output that is not needed. As a consequence, it leads to excessive lead time and it may also lead to situations where defects are not detected and products are deteriorated

(Bicheno & Holweg, 2009). So whatever the reason, making a quantity of products that exceeds the demand is wasteful. Waste from overproduction is also difficult to identified unless the quantity of products sold is compared to the quantity shipped (Nicholas, 2010).

2.3.5.2. The waste of waiting

This waste is related to flow and it takes many forms like waiting for materials or orders from preceding processes. It may also occur in automated processes when an operator who turns on a machine after having loaded it, remains in front of the machine and waits for the end of the process (Nicholas, 2010). Waiting is a waste that must be avoided as it results into reduced productivity and efficiency. Indeed, it causes longer lead times and it may also decrease engagement and motivation of employees (Helmold, 2020).

2.3.5.3. The waste of unnecessary motions

Unnecessary motions is the excessive movement of material or machines within the work area. It leads to higher cost due to the decrease of productivity. This is due to the fact that unnecessary motions require more time or capacity in operations than actually required in a process where unnecessary movements are eliminated (Helmold, 2020).

2.3.5.4. The waste of transporting

Any movement of materials can be considered as a waste because the customer does not pay for having goods moved around. In addition to that, the likelihood of damage increases with the number of operations of material handling and transport (Bicheno & Holweg, 2009).
However, this waste cannot be fully eliminated. The supply of goods on a market requires a minimum of transport from the manufacturing to the delivery to the final customer.

2.3.5.5. The waste of overprocessing

Overprocessing is related to activities and processes which are more than the customer expects or needs. In other words, adding more value than the customer requires is a waste of overprocessing. Simplification of the activities reduce these wastes (Helmold, 2020).
The origin of this waste seems less intuitive. Indeed, why does a company put energy on processes which the customer does not pay for? Some possible reasons could be inappropriate

or not capable processes that require additional work in order to meet the expectations of the customer.

2.3.5.6. The waste of unnecessary inventory

Inventory can be classified in three types: raw material, work in process (WIP) or semi-finished goods and end items. Their causes of existence and priorities for decrease are quite different. Inventory in raw material may be necessary due to constraints at supplier level while the inventory in end items helps to adapt to market in case of customer demand increase. But in general excessive inventory is a waste as it represents a risk of obsolescence (Bicheno & Holweg, 2009), items are waiting for something to happen which represents a situation where costs are generated and time is lost since no value is being added to them (Nicholas, 2010).
In Lean, the reduction of inventory is not an end in itself but it must be considered as an opportunity for exposing wasteful practices as shown in the analogy of a ship on water where inventory is compared to water depth and where problems like poor scheduling, quality issues, machine breakdown or long changeover are huge boulders into the sea (Nicholas, 2010).

2.3.5.7. The waste of defects

Defects impact the quality of products which deviate from the standards of their design or from the customer's expectation. Defective products must be replaced and require additional work to process it. In some circumstances, it may cause as well loss of customers (Helmold, 2020).
Product defects are ideally detected and handled before products are released on the market. However this activity represents also a waste because correcting defects increases production lead times which can lead to other delays in the process (Nicholas, 2010).

The results of waste reduction can be measured by efficiency indicators and among the most used metrics are lead time, on-time delivery, Overall Equipment Effectiveness, WIP and many others (Chiarini, 2012).
The presentation of the seven wastes ends this introduction about what is Lean. The choice of the TPS house as core concept allows to approach the ultimate aim of Lean through a global view. It describes also Lean as a complex system in which every single element contributes to the whole. Before to discuss the spreading of Lean in Six Sigma philosophy and in the Supply Chain discipline, it is important to present two configurations in which Lean can be deployed: the mechanistic and the organic systems.

2.4. A mechanistic or organic deployment of Lean

The purpose of this paragraph is not to develop organizational models theories but rather to differentiate two models for Lean deployment by referring briefly to the metaphors of organism and machine. Achieving a level of quality that meets exactly the customer's needs by eliminating all the non-added values in the process is the continuous strategic target undertaken by Lean. This can be made possible with strong commitment from members (c.f. the importance of culture in TPS). In order to comprehend the metaphors of organism and machine, this section will refer firstly to Spencer research works who assessed the place of quality and employees in mechanistic and organic systems. Secondly, the characteristics of mechanistic and organic Lean will be described based on Liker (2020) input to those notions. Some similarities should then come out. For Spencer (1994), the definition of quality under the mechanistic model relates to a conformance to internal standards, in other words the product or service is fine if it works. Under the organic model, customers satisfaction would be emphasized by taking into account their needs. Regarding the role of employees, under the mechanistic model, employees would be more passive, follow orders whilst under the organic model, the job is done because employees are committed to a common purpose. In organic model, motivation is driven by a vision. For Liker (2020), the deployment of Lean "mechanistically" or "organically" leads to two approaches with a significative difference in their characteristics. Mechanistic Lean would be faster to implement with short-term efficiency while the organic Lean would be more sustainable as it is based on deep learning and process ownership.

When they talk about mechanistic and organic systems, there is a certain consistency between the models presented by Spencer (1994) and the deployment of Lean suggested by Liker (2020). The most important factor is the people engagement which is very low for example in mechanistic model and mechanistic deployment of Lean. In terms of quality, there is also similarities about how quality is perceived from a mechanistic or an organic point of view. As an example, mechanistic Lean will address a quality issue in the context of a project and not because of continuous improvement culture. It fits in with the perception of quality in mechanistic model described by Spencer (1994). Indeed, until the quality is fine as per the internal standards there is probably no need to launch a project for improving a process in any form.

In the next sections, some others concepts of Lean that exist beyond the traditional Toyota System framework will be reviewed.

2.5. Lean Six Sigma

In the next sub-sections, the concept of *six sigma* (from a process point of view) will be discussed as it is a discipline that is frequently combined with Lean thinking in order to form Lean Six Sigma (LSS) which is deployed in those industries supporting Operational Excellence programs.

2.5.1. What is Six Sigma?

The Six Sigma philosophy works under a structured problem-solving approach whose aim is to eliminate variability, defects, and waste in a process. This structure is called Define–Measure–Analyze–Improve–Control (DMAIC), where

(i) Define is for the definition of the problem that needs to be addressed;
(ii) Measure is for the measurement of the problem and the process from which it was produced;
(iii) Analyze is for the analysis of the process to identify the root causes of defects and the opportunities for improvement;
(iv) Improve is for the improvement of the process;
(v) Control is for the implementation and the control of the improvements.

The majority of decision-making tools for Six Sigma are borrowed from statistics (Muralidharan, 2015). Indeed, Six Sigma has an approach based on facts and data. All the results of the project are validated using ‘sigma level’ around the target. This sigma level can be put in correlation with the number of defects in a process and the cost of poor quality (CPQ) (Chiarini, 2012).

2.5.2. From Lean to LSS

Similarities can be seen between DMAIC and the Kaizen cycle (PDCA) from Lean. Both problem-solving approaches are made of steps coming one after another with the goal of achieving an improvement of the process. However Kaizen is more dynamic than DMAIC as it is a continuous improvement philosophy while DMAIC is deployed and exists in the context of a well-defined project.

As Lean focuses on streamlining a process by identifying and removing wastes, combining Lean and Six Sigma modifies the DMAIC approach by emphasizing speed. Wastes like rework and scrap are often the result of variability in the process. So there is an opportunity for connecting Six Sigma and Lean to form LSS whose the goal is to supply quality products that meet customer requirements as effectively and efficiently as possible (Muralidharan, 2015). But isn't what Lean seeks to achieve already? Certainly but the use of statistical tools for data analysis and process control brings more accuracy. Six Sigma can also be considered as a prerequisite for Lean that needs process stability to work which is exactly what Six Sigma aims for (Friedli, Mänder & Bellm, 2013). Figure 2.3 illustrates the interaction between Lean and Six Sigma.

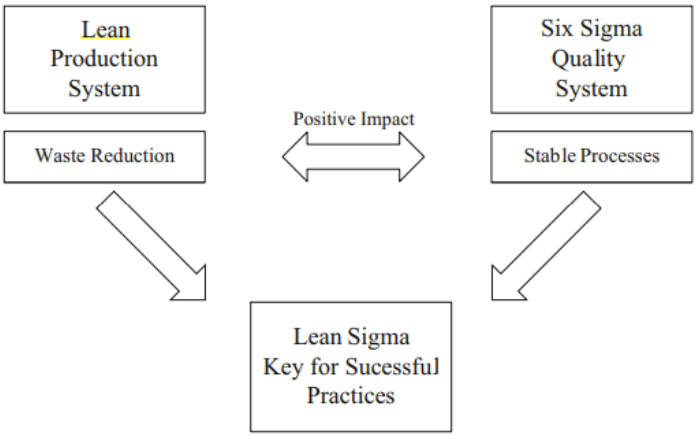


Figure 2.3 - Interaction between Lean and Six Sigma (adapted with permission from Friedli & al., 2013, p.301)

2.6. Lean in the Supply Chain Management

In this section, the application of Lean in the Supply Chain as well as the barriers for its implementation will be presented. But first of all, it is necessary to define what is Supply Chain.

2.6.1. What is Supply Chain?

According to Ballou, "The Supply Chain comprises all activities related to the flow and transformation of products and information, starting from raw materials to the end user, both downstream and upstream in the Supply Chain" (as cited in Ledoux Takeda Berger, Tortorella & Rodriguez, 2018, p. 40).

This is a another definition of Supply Chain that brings more details:

> A Supply Chain consists of all parties involved, directly or indirectly, in fulfilling a customer request. The Supply Chain includes not only the manufacturer and suppliers, but also transporters, warehouses, retailers, and even customers themselves. Within each organization, such as manufacturer, the Supply Chain includes all functions involved in receiving and filling a customer request. These functions include, but are not limited to, new product development, marketing, operations, distribution, finance, and customer service (Chopra, 2019, p.15).

The goal of Supply Chain is to satisfy the needs of the customers and to generate profit. There are three key flows allowing the functioning of a Supply Chain: products, funds and information. It must have also the objective to maximize the net value created which is the difference between the value of the final product for the customer and the costs generated in the entire Supply Chain in order to fill the customer's request (Chopra, 2019).

Based on these definitions of Supply Chain, Lean is a philosophy that may find its place and play a role in the functioning of Supply Chain. Indeed, both disciplines are customer-oriented with special attention to the management of products and information flows. So for all the aspects impacting the quality, Lean and Supply Chain are compatible. In what follows, the matters included in the Supply Chain process that are not quality related will be hence excluded like for examples Finance or Marketing as quoted in the definition of Chopra (2019).

2.6.2. Lean Supply Chain Management

Now that Lean and Supply Chain have been defined, how Lean Supply Chain Management (LSCM) can be characterized? LSCM can be described as a set of entities linked by upstream and downstream flows of services, products and information that work jointly to reduce waste by pulling only what is needed to meet customer's needs (Vitasek, Manrodt & Abbott, 2005).

In LSCM, the flow of products and information from raw materials suppliers to the delivery of products to final consumer is considered as an integrated whole. But what is the difference with Lean vision of TPS? Indeed the goal of JIT which is one of the pillar of TPS is to make the flow of products (and by extension the flow of information) before, during and after the manufacturing process more efficient. Hence, TPS includes already aspects related to the delivery of materials or products from supplier to the final user. Actually, the main difference

could be that LSCM is very heterogeneous depending of the industry while TPS finds its roots in the automotive sector and has been developed according to the characteristics of this sector.

2.6.3. The barriers for Lean Supply Chain implementation

The LSCM approach differs from the "trading objective", in which profit depends on the ability to negotiate with customers or on market prices. It is a strategy based on a long term involvement of Supply Chain partners, with a lot of cooperation and systematic waste elimination along the process chain (Yusuf et al & Agarwal et al., as cited in Tortorella, Miorando & Marodin, 2017).

This strategy may encounter barriers making it difficult to achieve the targeted improvement. Applying Lean principles to Supply Chain activities is a difficult process due to the fact that waste is not easy to be identified and quantified in an entire chain where process is complicated to be controlled from suppliers to customers (Anand & Kodali, Soni & Kodali, as cited in Tortorella et al., 2017). Parallel to the identification of these difficulties or barriers for the implementation of Lean in Supply Chain, it would be interesting to know also what are the main Lean practices used in Supply Chain.

Ledoux Takeda Berger et al. (2018) performed a systematic literature review that identified in various sectors the main LSCM practices and barriers according to the frequency they were cited. A total of eighteen practices and twelve barriers have been identified. Table 2.1 gives ten practices and ten barriers identified by this search.

Table 2.1 – Practices and barriers in LSCM (adapted with permission from Ledoux Takeda Berger et al., 2018, p. 47-54, 57-59)

Lean practices in LSCM	Barriers for LSCM implementation
Kanban or pull system	Difficulties for cultural changes
Value Stream Mapping or Value Chain Analysis	Complexity of the Supply Chain
Close relationship between stakeholders	Lack of trust in Supply Chain partnerships
Use of information technology to integrate the flow of information along the Supply Chain	Lack of collaboration and involvement of the entire Supply Chain

Lean practices in LSCM	Barriers for LSCM implementation
Development of Supply Chain KPIs	High oscillation of demand
Efficient and continuous replenishment	Lack of commitment of senior management
Standardized work procedures for quality purpose	Lack of Information and Communication Technology (ICT) infrastructure for integration
Problems solution (feedback for shared solutions)	Low understanding of concepts and principles related to LSCM implementation
Continuous improvement	Lack of availability of resources
Keiretsu (relationship based on trust)	Low information sharing

Table 2.1 – Practices and barriers in LSCM (adapted with permission from Ledoux Takeda Berger et al., 2018, p. 47-54, 57-59)

Lean practices in LSCM as mentioned in Table 2.1 are very similar to most of the TPS pillars, in particular JIT and operational stability. There are also some links with LSS practices when referring to the use of KPIs and Value Stream analysis. However it becomes more interesting when the barriers are reviewed. Indeed, some elements quoted among the barriers for the implementation of LSCM find their remedies in the main Lean practices in LSCM. An example is the lack of collaboration and information sharing versus the use of ICT to integrate the flow of information. The heterogeneity of the industries in terms of Supply Chain practices may explain that a Lean practice used in one sector is considered as a barrier in another sector.

2.7. Conclusion

The aim of this Part 2 was to introduce Lean and its extensions to Supply Chain without getting a strict vision of what it is. The sector that will be analyzed in the next parts is the pharmaceutical sector which is a sector that may be in some instances very different from the automotive sector that influenced the TPS and hence the Lean philosophy. The founding principles of TPS are very important concepts that form a consistent whole allowing to reach high level of quality in processes while eliminating the non-adding values activities considered as wastes. The implementation of Lean mechanically or organically has been discussed as well. Organic Lean support the idea that commitment and strong culture of continuous improvement

are needed in order to sustain any improvement that could have been reached by a mechanistic Lean approach. In this sense, Six Sigma extends the range of tools that can be used in mechanistic approach of Lean for managing the quality of the processes. Finally, LSCM has been explained through some practices and barriers in its implementation.

3. The Pharmaceutical Industry

3.1. Introduction

In this Part 3, the pharmaceutical sector will be described. After a presentation of the industry including figures, an overall view of the manufacturing process will be given in order to understand the complexity of the entire chain from the supply of raw materials to the final shipping of finished products. Finally, some critical elements of the good practices to respect in the manufacturing of pharmaceutical products will be reviewed.

3.2. Presentation of the Pharmaceutical Industry

The Pharmaceutical Industry is characterized by organizations, operations and processes involved in the discovery, development and the manufacturing of drugs (Shah, 2004).

Before to analyze further the key players involved in the operations, it may be appropriate to give a definition of a drug. The World Health Organization (WHO) defines a drug as:

> any substance or mixture of substances manufactured, sold, offered for sale or represented for use in the diagnosis, treatment, mitigation or prevention of disease, abnormal physical state or the symptoms thereof in man or animal; [and for use in] restoring, correcting or modifying organic functions in man or animal (as cited in Shah, 2004, p. 929).

The Pharmaceutical Industry is very complex as it involves challenges to coordination among multiple actors. According to Shah (2004), there are five categories of players in the Pharmaceutical Industry, including:

(i) The companies with Research and Development (R&D) activities and manufacturing sites in many locations;
(ii) The generic manufacturers, who produce out-of-patent products and over-the-counter products;
(iii) Local manufacturing companies operating in their home country, producing both generic products and branded products under license or contract;
(iv) Contract manufacturing organizations (CMO) who provide outsourcing services for the production of active ingredients (AI) or final products;

(v) Biotechnology start-up with no significant manufacturing capacity;

Taking into account the entire chain of pharmaceutical products supply, it would be appropriate to add to this list three other key players:

(vi) The companies who supply materials that do not enter in the composition of the pharmaceutical product but necessary for the manufacturing of the products (e.g. disposables, devices, calibration standards for the equipment);
(vii) The companies providing outsourcing services for quality control purpose;
(viii) Transport companies when the transport activity is outsourced.

Now that the main actor have been presented, some figures can be used to show the weight of this industry compared to other industries in terms of investment and also how the world-wide sales are broken down. Table 3.1 gives for 2019 an overview of the amount of the investment in Europe for 2500 world companies aggregated by industrial sectors.

Rank	Sector	R&D in 2019, € bn	1-year change, %	Net sales, € bn	1-year change, %	R&D intensity, %
1	Pharmaceuticals and biotechnology	166.8	10.0	1043.9	7.5	15.4
2	Software and Computer Services	142.7	20.6	1212.6	11.2	11.8
3	Technology Hardware & Equipment	139.6	8.9	1557.1	0.3	9.0
4	Automobiles & Parts	132.7	1.9	2749.4	-1.0	4.8
5	Electronics	68.9	6.3	1352.1	1.8	5.1
6	Industrial Engineering	32.5	6.4	996.4	3.9	3.3
7	Chemicals	23.1	-3.2	964.9	-4.3	2.4
8	Aerospace & Defense	20.6	4.3	518.4	6.4	4.0
9	General Industrials	20.4	0.5	672.1	0.1	3.0
10	Construction & Materials	19.2	20.3	1048.9	9.8	1.8
11	Health Care Equipment & Services	18.9	9.3	495.1	8.1	3.8
12	Leisure Goods	16.5	3.5	269.6	-1.1	6.1
13	Banks	11.4	5.6	351.7	0.4	3.2
14	Oil & Gas Producers	9.9	5.2	2725.5	-3.3	0.4
15	Household Goods & Home Construction	9.0	3.5	360.6	4.6	2.5
Total 38 industries		**904.7**	**8.9**	**21039.9**	**1.9**	**4.3**

Table 3.1 – R&D Investment in Europe (adapted with permission from Publications Office of the European Union, 2020, p. 110)

Pharmaceuticals and Biotechnology represent the leading industry in terms of absolute value for R&D investment. The indicator "R&D intensity" must be understood as the R&D investments as percentage of net sales in 2019. So with a R&D intensity of 15,4%, this industry has as well the largest spending as a proportion of sales.

Regarding the sales, the pharmaceutical market was worth € 943,667 million at ex-factory prices in 2020 with the North American market as the world's largest market where almost half of sales were recorded. Europe is the second world's largest market followed by Asian markets (European Federation of Pharmaceutical Industries and Association [EFPIA], 2021)

Figure 3.1 shows the breakdown of the world pharmaceutical market based on sales registered in 2020.

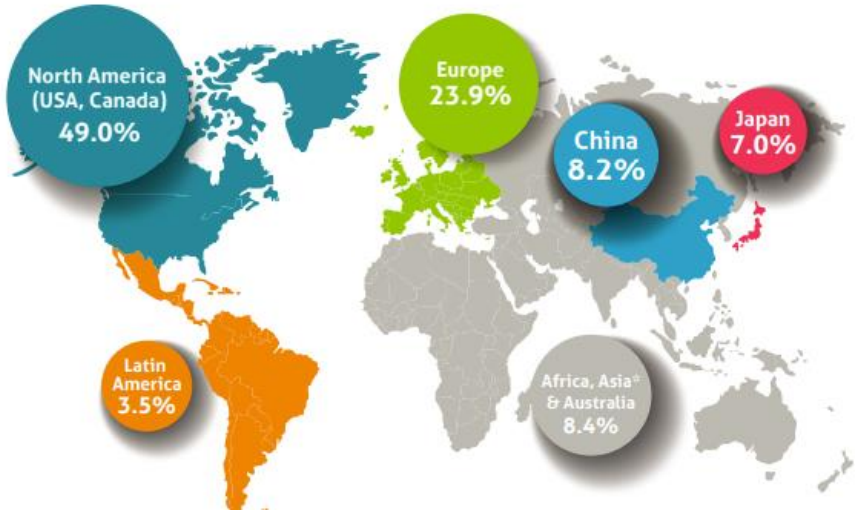


Figure 3.1 – Breakdown of the world pharmaceutical market – 2020 Sales (adapted with permission from IQVIA as cited in EFPIA, 2021, p. 14)

The Pharmaceutical Industry can definitely be considered as a dynamic industry for its role in discovery of new drugs. There is no other industry investing as much in R&D projects. But the Pharmaceutical Industry is also very complex and sophisticated and this will be further discussed in the next sections.

3.3. The Pharmaceutical Supply Chain

The Pharmaceutical Supply Chain management for clinical and development programs differs from the one for commercial products in which R&D stage is completed, processes are validated and drugs are approved for use on the market.

It is the Pharmaceutical Supply Chain for commercial products that will be discussed further here. Figure 3.2 illustrates the different development phases of a vaccine. The phase IV or Pharmacovigilance (PV) corresponds to this commercial phase which requires also assessment of the product's safety from the manufacturer.

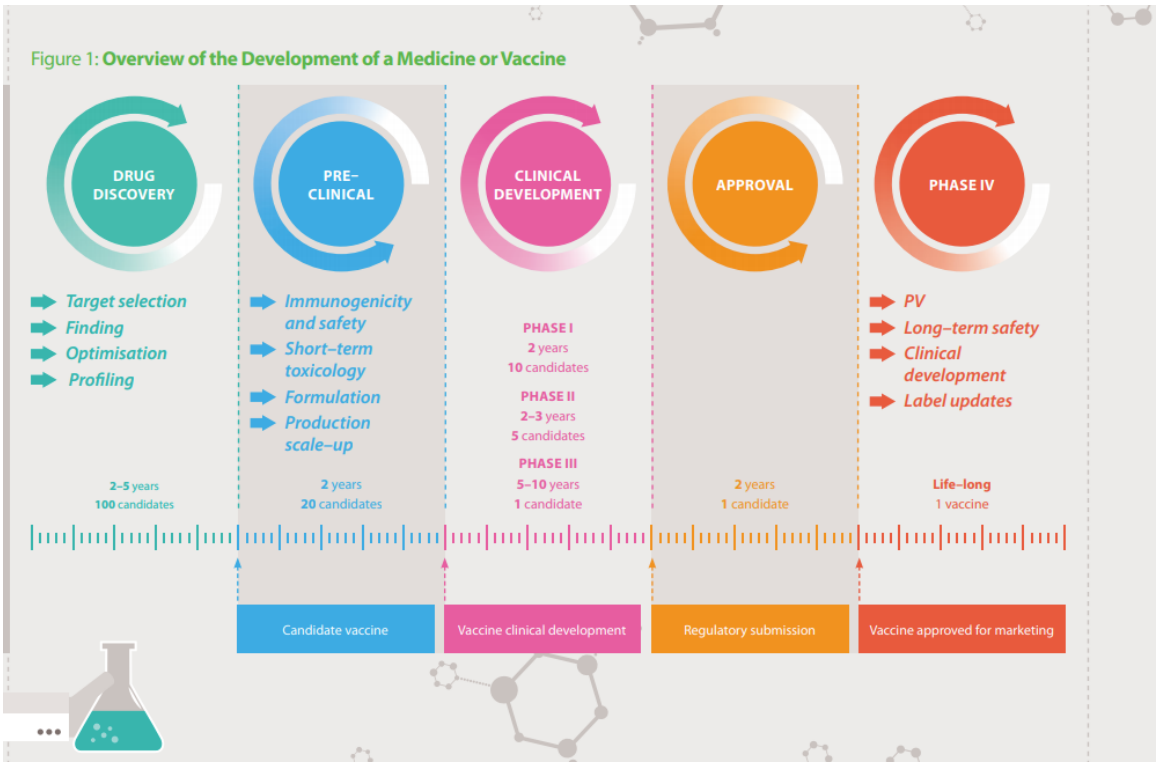


Figure 3.2 – Overview of the Development of a Vaccine (adapted with permission from International Federation of Pharmaceutical Manufacturers & Associations [IFPMA], 2019, p.4)

Shah (2004) considered the Supply Chain in Pharmaceutical Industry as being composed by:

(i) Primary Manufacturers;
(ii) Secondary Manufacturers;
(iii) Distributors;
(iv) Retailers and Hospitals.

The above breakdown is very common in Supply Chain for commercial products. Patients can be included in this chain as well as the suppliers of materials for primary and secondary manufacturing steps and any organization providing support activities (e.g. quality control services).

The primary manufacturing site is responsible for the production of the Active Pharmaceutical Ingredients (API). This process may involve chemical synthesis, fermentation, purification and separation stages for building up the complex molecules. The secondary manufacturing site is responsible for the production of the final product and also for the final packaging step (Shah, 2004). For illustrating the complexity of the operations in the Pharmaceutical Industry as well as their sequence and the connections between them, the production of a commercialized vaccine can be taken as example. A vaccine production process is broken down into eleven steps (Sanofi, 2017):

(i) Bacteria, virus or cell culture: the antigens are developed;
(ii) Harvesting: the antigens produced in the previous step are extracted;
(iii) Purification: impurities are removed by the use of physical and chemical processes;
(iv) Inactivation: only immunological properties of the product are retained. The pathogenicity is suppressed;
(v) Valence assembly: the active substances are put together in a single component;
(vi) Formulation: the active substances and excipients are melt together;
(vii) Filling: the formulated substance is filled into vials or syringes;
(viii) Freeze-drying: the liquid is transformed into powder for better stability and conservation;
(ix) Packaging: the vaccine is labeled and packed for shipping;
(x) Batch release: The product is certified as having been produced in conformance with the quality requirements. The vaccine can be released for distribution on the market;
(xi) Transport: the product is distributed respecting the cold chain. Validated low temperatures contributes to the stability of vaccines.

The primary manufacturing and secondary manufacturing as defined by Shah (2004) correspond respectively to steps one to five and steps six to nine of the vaccine production process.

In the Pharmaceutical Industry, these steps are most commonly classified as being part of the Upstream Process (USP) or the Downstream Process (DSP) that starts immediately after the virus or cell culture or the formulation/filling/packaging stages (Rees, 2011).

It is worth recalling that all these manufacturing steps presented in the context of a vaccine manufacturing (USP, DSP, Formulation, filling/packaging) can be outsourced to one or several

third-party organizations when not performed by the manufacturer that places the final product on the market. There are some very recent examples in the context of Covid 19 pandemic that show the use of outsourcing for the manufacturing of candidate vaccines. Companies like AstraZeneca (Catalent, 2020) Johnson & Johnson (Catalent, 2021) or Moderna (Roy & D'Silva, 2021 & Lonza, 2021) have turned to CMOs for outsourcing USP, DSP, formulation and filling/packaging processes of their vaccines.

For the analysis about Lean in Pharmaceutical Supply Chain, the focus will be done only on the activities involved in the transformation of the product and hence the processes related to the distribution of final products from distributors to retailers/hospitals and end users will be not analyzed. This focus corresponds to the primary activities of the generic value chain from Porter (1985) and specially to the following three elements:

(i) Inbound logistics which are the activities associated with receiving and storing all the inputs required for the operations;
(ii) Operations which are the activities that transform inputs into outputs (e.g. USP, DSP etc..);
(iii) Outbound logistics which are the activities related to shipping and warehousing.

A fourth element can be also taken into account which is:

(iv) Procurement that is considered as a support activity. Procurement relates to the purchase of inputs such as raw materials, machinery, equipment and production consumables (Rees, 2011). Procurement has a direct impact on the inventory policy which is a key element in Lean.

When activities required for the production of the final drug are outsourced, the pharmaceutical Supply Chain becomes quite complex. Its performance will depend of how procurement, inbound/outbound logistics and operations activities are managed at the level of each actor of the chain. These four elements from the Porter value chain are duplicated as many times as there are actors and processes involved in the transformation of the product.

Before tackling in Part 4 the implementation of Lean in the Pharmaceutical Supply Chain for assessing its contributions and limits, it is necessary, before to close this part, to approach the good practices to implement and respect in the manufacturing of drugs.

3.4. The Good Manufacturing Practices in the Pharmaceutical Industry

The major difference between pharmaceutical manufacturing and other types of manufacturing is that pharma has to follow Current Good Manufacturing Practices [CGMPs]. CGMPs is a set of regulations, codes, and guidelines for the manufacture of drug substances and drug products, medical devices, in vivo and in vitro diagnostic products, and foods. These set of principles and procedures, when followed by manufacturers of pharmaceutical products, helps ensure that the products manufactured will have the required quality (Basu, Friedli & Bellm, 2013).

For the European Union [EU], EudraLex is the collection of rules and regulations governing medicinal products for human use as well as for veterinary use. It consists of ten volumes. Eudralex - volume 4 contains guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively (European Commission, 2015). In US, Code of Federal Regulations (CFR) contains in Title 21 an interpretation of the Federal Food, Drug and Cosmetic Act and related statutes. The pharmaceutical or drug quality-related regulations appear in several parts of Title 21 (Food and Drug Administration [FDA], 2020). Other regulations and rules exist as well outside US and EU but even if some minor differences may appear between them, it can be assumed that they all have a significative common base.

In the rest of this section, references to some parts of Eudralex – volume 4 will be done. These elements will be selected based on the influence they may have on the four key elements of the value chain identified previously which are procurement, inbound logistics, operations and outbound logistics. There are three major topics approached in Eudralex – Volume 4 that are very relevant in this regard: Process validation, outsourcing and the handling of materials and products.

3.4.1. Process validation

Validation is essential to demonstrate that if the drug was made using a well-defined process in a certain equipment configuration, the right product will be made with the required level of quality (Basu et al., 2013).

Annexe 15 of Eudralex – Volume 4 (European Commission, 2015) outlined the requirements and principles applicable to the manufacture of all pharmaceutical dosage forms. It covers the

initial validation of new processes, subsequent validation when processes are modified, site transfers and ongoing process assessment. In a traditional validation approach, a number of batches of the finished product are manufactured and supplied under routine conditions to confirm reproducibility. Five areas require specific attention in terms of validation/qualification:

(i) Validation of transportation: Finished medicinal products, bulk product or samples should be carried from manufacturing sites in compliance with the conditions defined in the marketing authorization, the approved label or product specification file. During transportation, continuous monitoring and recording of any critical environmental conditions such as temperature should be performed as well;

(ii) Validation of packaging: Variation in packaging equipment may have a significant impact on the integrity and correct operating of the product. Hence, primary and secondary packaging equipment for finished and bulk products should be qualified;

(iii) Qualification of utilities: The quality of steam, water, air, etc. produced by qualified installation should be confirmed;

(iv) Validation of test methods: All analytical test methods used in qualification and validation should be validated with appropriate limits set for defining the conformity of the results;

(v) Validation of cLeaning: In order to confirm the efficacy of any cLeaning process for all product contact equipment, a cLeaning validation should be performed;

The requirement to avoid cross contamination between the drugs being manufactured or with any external impurities is another key reason that explains the complexity and high cost of pharmaceutical manufacturing. Contamination may cause severe risk health of patients using pharmaceutical products (Basu et al., 2013).

3.4.2. Outsourced activities

Chapter 7 of Eudralex – Volume 4 (European Commission, 2015) provides guidance on outsourced CGMPs activities. The principle is that any activity subject to CGMPs requirements that is outsourced should be appropriately defined and monitored in order to avoid misunderstandings which could lead to processes of unsatisfactory quality. A written Contract must clearly establish the obligation of each party.

According to Basu et al. (2013), outsourcing is on the increase in the Pharmaceutical Industry facing severe cost pressure. Rather than investing in technology, quality and innovation in manufacturing to decrease cost, the industry is looking for cheaper labor sources (e.g. in India or in China) by outsourcing some activities.

3.4.3. Handling of materials and products

Chapter 5 of Eudralex – Volume 4 (European Commission, 2015) provides a set of recommendations regarding the handling of incoming materials and (semi) finished products. Among these recommendation, one deserves particular attention for its potential impact on the inventory. CGMPs require that incoming materials and (semi)finished products should be physically or administratively quarantined immediately after receipt or processing. Their use or distribution is allowed only if they are conform based on a quality review.

3.5. Conclusion

The aim of this Part 3 was to provide an overview of the Pharmaceutical Industry. The financial data related to R&D investments and sales shows its relative weight to other industries and confirm the dynamism in the Pharma research area. Then, the entire chain has been described through the key players and the different processes involved in the manufacturing of drugs making this chain very complex. Finally, some key elements of the CGMPs have been highlighted. Their potential impact on the value chain and hence the Pharma Supply Chain performance is tangible and will be further analyzed in Part 4.

4. How can Lean improve the pharmaceutical Supply Chain?

4.1. Introduction

In this Part 4, an evaluation of the weakness of the Supply Chain in Pharmaceutical Industry will be done by the identification of the elements that may cause poor performance in the delivery of drugs in terms of quality, quantity and time. Then, some practical cases of Lean implementation in Pharmaceutical Industry will be presented while identifying the nature of the problem they solved. Finally, the barriers for Lean implementation that are specific to the pharmaceutical Supply Chain will be discussed.

4.2. The Supply Chain performance in the Pharmaceutical Industry.

In this section, focus is made on the supply of commercialized product which is a post-approval activity (c.f. Figure 3.2). According to Rees (2011), many Supply Chains in many sectors fail to perform adequately and the pharmaceutical sector does seem to concentrate most of the issues of poorly performing Supply Chains in general and even more due to the specificities of this industry like:

(i) Supplier selection: it may take time to identify the appropriate suppliers based on all the regulatory requirements imposed by CGMPs and also to build a strong relationship;

(ii) Outsourcing: For drug product manufacturing, it may represent a potential issue in terms of quality and it may increase the manufacturing cycle time in case of lack of coordination between the actors. The regulatory aspect has also a huge impact on this practice (c.f. Part 3);

(iii) The regulatory framework: the procedures to follow for strict regulations compliance are highly complex and influence the industry practices. A non-compliance result for any test performed during the manufacturing of a product may lead in the best-case scenario to a delay in batch release and in the worst-case scenario to the rejection of the batch.

Poor quality and lack of coordination at all the stages of the Supply Chain seems to be the main factors responsible for the poor performance of the Pharmaceutical Supply Chain. Recent quality issues and vaccines shortage events highlighted the fragility of the

Pharmaceutical Supply Chain. The following two examples are very enlightening regarding this:

(i) In late 2007, contaminated product made of heparin led to dozens of deaths and hundreds of serious adverse events in various countries. Several pharmaceutical companies had to recall batches of drug as a preventive measure. Following these recalls, Competent Authorities traced back the Supply Chain ending up in China. A plant in Changzhou was identified as the supplier of the poor quality heparin active ingredient (Hedlund, Coyne, Sanford & Huddelson, 2012);

(ii) More recently in January 2021, AstraZeneca announced cuts in its supply of vaccines to the EU in the first quarter. It represented for March delivery, a reduction of 60% of the expected quantity. The reason given by AstraZeneca to EU officials was a production issues in Belgium where ThermoFisher manufactures the vaccines for AstraZeneca as a third-party partner. ThermoFisher explained that the drop in expected doses was due to a lower than anticipated yield from the base ingredients and also that the company sends vaccines to an Italian facility for secondary manufacturing before delivering to clients (Guarascio, 2021).

4.3. The benefits of Lean in the Pharmaceutical Supply Chain

By reducing wastes in processes and trying to reduce the variability in terms of quality and process cycle time, Lean can significantly improve the Pharmaceutical Supply Chain which struggles to provide good results. For example, when no attention is paid to the process flow in the manufacturing of a vaccine which is made of no less than eleven stages (Sanofi, 2017), the wastes and problems of coordination generated throughout the process can seriously impact the Supply Chain. The more complex the process is, the more the benefits of Lean are. In the Pharmaceuticals Industry the processes are very complex and long. The production of a commercialized vaccine takes at least six months according to Sanofi (2017). Lean brings a complete approach that challenges continuously the processes put in place. Two cases of Lean implementation in the Pharmaceutical Industry will be presented for illustration in the next two sub-sections. The mechanistic or organic nature of these implementations will be assessed as well as the problems they aimed to address.

4.3.1. The birth of cLEAN® at Novo Nordisk

cLEAN® is the LEAN philosophy program implemented at Novo Nordisk which the aim was to minimize waste and optimize production flow. The ‘c’ stands for ‘current’ meaning that it is a continuously improved program that is adapted to different areas in Novo Nordisk (Novo Nordisk, 2010).

From 1998, Novo Nordisk Product Supply (PS) capabilities came under pressure due to an increase of the demand and became a focus area. From 1998 to 2003, investments allowed extension of the capacity and the number of employees involved in product supply doubled from approximately 4,000 to 8,000. During this period, Novo Nordisk PS experienced challenges caused by cases of back orders or long delivery times. In this challenging time, Management started discussing measures that could be taken to increase capacity and improve the operational efficiency without investing more. This led to talks about waste reduction and Lean. Finally, on October 31st 2003 Product Supply Management launched cLEAN® (Mejlvang, 2013).

The general outlines of the cLEAN® at its start can be summarized in four phases (Mejlvang, 2013):

(i) The creation of a central cLEAN® Office with dozens of consultants who were in charge of driving and supporting the transformation process. Each production unit appointed its own cLEAN® responsible and employees from all the departments were dedicated to cLEAN® activities. It is a phase to enhance and impulse the project;

(ii) Setting of measurable targets: as an example, Cost of Goods Sold (COGS) in Product Supply was 28.3 % in 2003. Novo Nordisk needed to reduce its COGS to improve competitiveness. Management had established a target for COGS at 20 % within 5 years. The objective was generally accepted and a key reason for this was that cost savings from the cLEAN® efforts through the new COGS target would be invested for developing and growing the company. Improvement of Novo Nordisk competitiveness also meant that jobs would be secured for the coming years;

(iii) cLEAN® Academy: the launch of a training and education program called “cLEAN® Academy” consisting of several levels of expertise (see Figure 4.1). From the introduction of the principles of the cLEAN® to Lean tools presentation

and projects handling, it has created a common framework for continuous improvement initiatives in the daily business;

(iv) PS@ShopFloor: all the team leaders and department managers were expected to spend a certain time on the shop floor every day. The idea behind this initiative was to create a problem solving and learning culture where problems are addressed quickly leading to more stable processes and hence operational excellence. This practice can be assimilated to Gemba which is the place of action in Lean philosophy. This Japanese word can be thought of in terms of the "four actuals": spend time at the actual workplace, observe the actual process, look at what is actually happening and gather the actual data (Bicheno & Holweg, 2009).

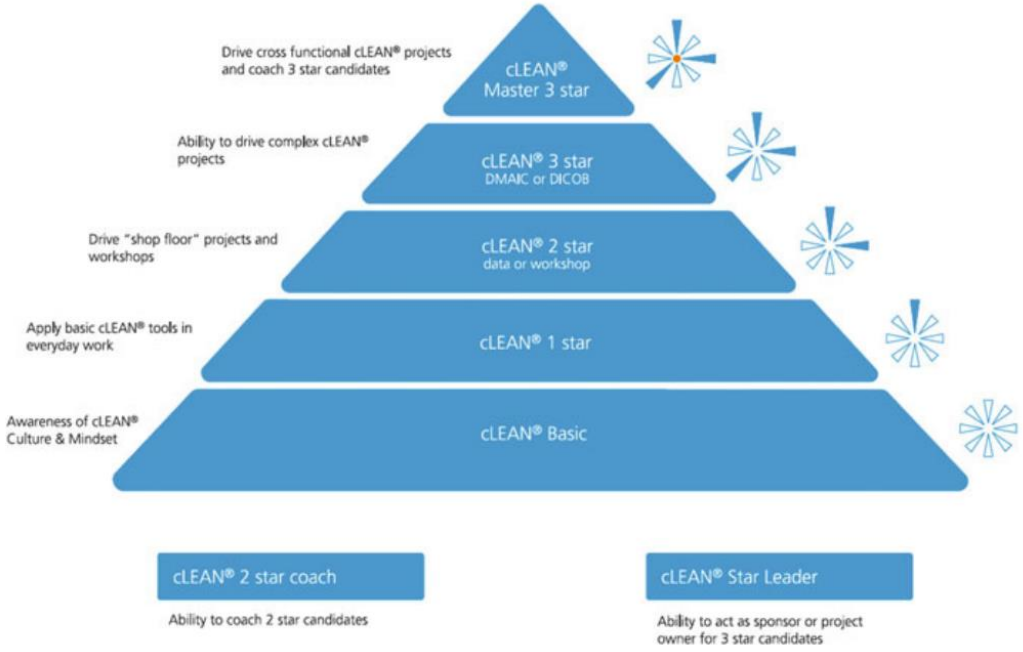


Figure 4.1 – The levels of Novo Nordisk's cLEAN® Academy (adapted with permission from Mejlvang, 2013, p. 135)

The communication of results is important to maintain commitment throughout the organization and cLEAN® has delivered significant business results in terms of quality, delivery and cost as illustrated in Figure 4.2. Culture requires the support of tools and without a strong culture, the effect of the tools may become negligible in their ability to solve the problems. This example of Lean implementation at Novo Nordisk is a good illustration of a balanced mix between the organic Lean and the mechanistic Lean approaches explained in Part 2. With cLean®, Novo

Nordisk invested as much in tools as in a program that impact the motivation and the commitment of the people involved in the heart of the processes.

4.3.2. Use of Lean for changeover time decrease in the Pharmaceutical Industry

Changeover (CO) reduction, also known in the Lean manufacturing field as Single Minute Exchange of Die (SMED), is a tool that reduces the set-up operations and consequently reduces WIP inventories (Chiarini, 2012). There are many views of CO and the widely held one is that it is the time from the last piece of a batch to the first good piece of the next batch (Bicheno & Holweg, 2009).

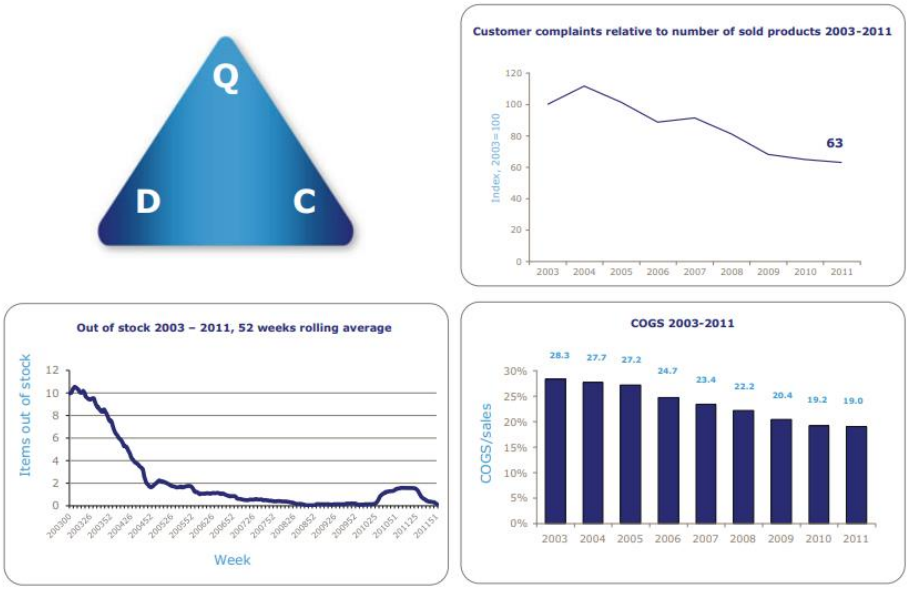


Figure 4.2 – Novo Nordisk - Results on quality, delivery and cost for the period 2003-2011 that corresponds to cLEAN® deployment (adapted with permission from Mejlvang, 2013, p. 141).

During the 11th International Conference Interdisciplinarity in Engineering which was held in October 2017 in Romania, a SMED project for CO time decrease in a certain bottles filling production line in the Romanian Pharmaceutical Industry was presented (Al-Akel, Marian, Veres & Horea, 2018). The main features and outcomes of this case are exhibited here below:

The targeted company needed to reduce CO times at a certain production line that had 37 CO processes to conduct annually with a mean CO time of 25,3 hours. The set target was shortening this time to 16 hours and stabilizing the process by implementing Lean Manufacturing – SMED tools.

The project followed the DMAIC structure (c.f. section 2.5.1.) After the define phase was completed, a measurement and analysis of the current process were performed in order to reveal the real process status and the causes for long CO. A significant standard deviation (sd) of the CO time was observed before improvement.

Through Gemba, the major root causes of this variability were identified. Some of these root causes were related to lack of visual controls, poor teamwork and communication, absence of set targets or wasted time on useless steps. Correctly identifying the root causes of inefficiency is the most important element when conducting an improvement process. For each root cause an adequate improvement was implemented on the shop floor. Visual management in this case highly contributed to the improvement of the CO time. It consisted mainly in the creation of a CO plan or poster for helping the production teams to perform standardized CO and also in a reorganization of the storage area for a better identification and to make easier the access to the different materials reducing this way wastes related to unnecessary motions.

The implementation of Lean Manufacturing – SMED tools on the production shop floor in this bottle filling process led to a significant decrease of the CO time from 25,3 hours to 17,8 hours. Figure 4.3 gives a view of the distribution of the process before and after improvement. In the form of histograms, it calculates the process capability. The targeted CO time represented by dotted green line is set at 960 minutes which corresponds to 16 hours. Lower Specification and Upper Specification Limits are set respectively at 800 and 1200 minutes. These limits are not calculated from the process but represent the ideal range of time for CO in terms of customer satisfaction.

Several key indicators may be generated during a process capability analysis. Four important indicators from Figure 4.3 are explained here below:

(i) Process mean: On average, the CO time was 1516,9 minutes before improvement. This average time was reduced to 1065,9 minutes after improvement;

(ii) Sd was 249 minutes before improvement and 178 minutes after improvement;

(iii) % out of specification: before improvement of the process, 90% of the COs were out of the specification limits. After improvement, 29% of the COs were out of the specification limits. In this SMED case, even after the improvement, the process limits set at average time +/- 3 sd still exceeded the specification limits: (1066

minutes – (3 x 178 minutes)) < 800 minutes and (1066 minutes + (3 x 178 minutes)) > 1200 minutes.

(iv) Cpk: this metric gives the actual capability of the process. It measures how well the process is centered between specification limits by calculating the following ratio: (Nearest specification – Average)/3*sd. In this case and after the improvement, Cpk= (1200-1065.9)/(3*177.56)= 0.25. A Cpk superior to 1 means that the process is well centered. In this example, the process has been improved and the Cpk has increased from -0.44 to 0.25. However it was still a process that is not capable from a Six Sigma point of view.

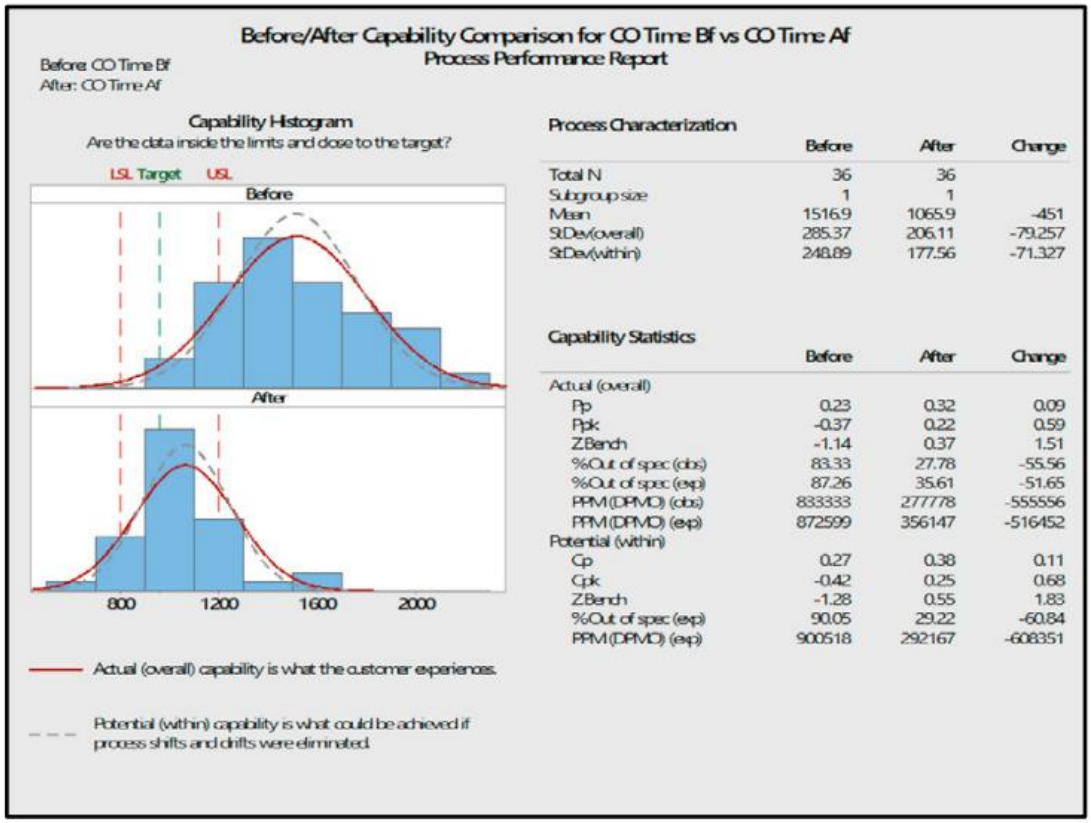


Figure 4.3 – CO Process capability before and after improvement (adapted with permission from Al-Akel et al., 2018, p. 891)

In this SMED project, wastes elimination and standardization of the work were key factors for the process improvement while for measuring the process performance before and after the improvement, six sigma control chart was used. It is typically a LSS approach that was used by the project owners. This SMED project differs from cLEAN® project presented in section 4.3.1 by its Lean approach that was purely mechanistic. The risk is high for this type of quick improvement to not last after some time due to lack of learning and low engagement.

4.4. The systemic barriers in the pharmaceutical Supply Chain for Lean implementation

The examples presented in previous sections demonstrate that Lean deployment in the pharmaceutical Supply Chain can help to achieve great results. It is probably more common to encounter this deployment in the activities related to operations due to the fact that Lean finds its origin in manufacturing. In this section, the five elements of the TPS will be reviewed considering the influence of:

(i) Process validation as imposed by CGMPs;
(ii) Materials and products handling as imposed by CGMPs;
(iii) Outsourcing which is a strategy widely used in the Pharmaceutical Industry.

The analysis will be presented in the form of a double-entry table (see Table 4.1). In each cell of this double-entry table, an assessment will be provided in order to identify the barriers for Lean deployment which are specifics to the Pharmaceutical Industry.

Table 4.1 – Influence of CGMPs and outsourcing on TPS

	Process validation	Outsourcing	Materials/products handling
Culture for continuous improvement	**It may be a barrier with moderate impact**: Process validation requires a scientific approach so for improvement related to critical processes, it may extend the continuous improvement cycle as any change must be validated.	**It may be a barrier with high impact:** outsourcing means a certain loss of control of the Supply Chain process so it is more difficult to ensure a culture for improvement through the chain as each partner has its own strategy.	**Not a barrier:** there is no obvious link between requirement for products handling and culture for continuous improvement.

Table 4.1 – Influence of CGMPs on TPS

Process stability	**Not a barrier:** the aim of process validation is the process stability.	**It may be a barrier with high impact:** outsourcing may cause negative impact on process stability due to the need for higher coordination between partners.	**Not a barrier:** quarantine and release of materials and products after testing guarantee a certain process stability.
Jidoka	**Not a barrier:** process validation is compatible with failures detection systems (e.g. validated camera on a production lines for quality control, the use of a temperature recorder during the transport of products or the training validation of the operators for candling activities).	**It may be a barrier with high impact:** the responsibility for defects detection is moved to the third-party partners for the outsourced activities. This may create a certain quality variability in case of failure at the level of third-party partners	**Not a barrier:** the requirement for products handling does not prevent the implementation of Jidoka.
JIT	**It may be a barrier with high impact:** process validation validates the entire cycle from raw materials reception to final product delivery. Operating outside this validated framework is not allowed/recommended so the process is complex and quite inflexible (e.g. materials are purchased from approved suppliers only).	**It may be a barrier with high impact:** outsourcing requires high coordination between partners in order to speed up the process, reduce the inventory and deliver the products when it is needed.	**It may be a barrier with high impact**: CGMPs require the quarantine of the materials, semi-finished and finished product until the release after it past quality control testing. This means for example that even quick delivery does not guarantee that the materials is allowed to be used in production.

Excellence in quality, cost and delivery through wastes elimination	**It may be a barrier with moderate impact**: once validation is performed, it is not allowed to simplify a critical process without performing a new validation. However, the wastes that are not subject to validation can be eliminated (e.g. unnecessary motions)	**It may be a barrier with high impact:** for all the reasons quoted above in this table, outsourcing may have high impact on the entire process excellence.	**It may be a barrier with moderate impact**: CGMPs impose the quality control of the products at each critical steps of the process. The positive side is that this requirement minimizes the risk of introducing poor quality products in the next production stage. The negative side of this control is the time it can take before the release of the products which can cause delay in the operations and hence generate a waste.

Table 4.1. – Table 4.1 – Influence of CGMPs and outsourcing on TPS

In Table 4.1, one characteristic of the Pharmaceutical Industry seems to have a potential influence on each element of TPS: outsourcing. In addition to that, one element of TPS was identified as being more complicated to implement in the Pharmaceutical sector: JIT.

4.4.1. The impact of outsourcing on Lean strategy

Outsourcing seems to be the most important barrier for the deployment of a Lean strategy throughout the Pharmaceutical Supply Chain. It has a potential negative impact on each element of TPS. It is important to talk about potential impact because in some cases, there may be good results generated by outsourcing strategies in terms of quality or cost. Outsourcing is a capacity or cost related decision so the reasons for outsourcing are not strictly incompatible with Lean.

But there are risks when any function is moved to a third-party partner. A broken Supply Chain process involving third-party partners makes the entire chain harder to control. It requires also a high level of coordination which the cost can be underestimated (Chopra, 2019).

Although CGMPs provide guidance which emphasize the importance of keeping a process under control when activities are outsourced, the risk of failure of the process is still present. The cases of contaminated heparin and cuts in the supply of Covid 19 vaccines presented in Part 3 are good examples to keep in mind.

4.4.2. The difficulty of implementing JIT in the Pharmaceutical Industry

The *romantic JIT* described by Zipkin as being a state with zero inventories, zero defect, lot sizes of one (as cited in Hopp & Spearman, 2001) is just not implementable in the Pharmaceutical Industry due to its systemic constraints:

(i) Suppliers of raw materials must be validated and comply with CGMPs requirements: this has a direct impact on procurement activities for example in case of out-of-stock condition in the supplier. Regarding out-of-stock situations, a strong relationship between manufacturer and its suppliers is crucial. When a manufacturer trusts in the capability of its suppliers to deliver the right quantity in a reasonable space of time (c.f. operational stability in TPS), an adequate level of inventory can be maintained avoiding storage of excessive raw materials;

(ii) Incoming materials and (semi-)finished products are placed in quarantine until release tests results are conform: It has a direct impact on inbound activities, operations and outbound activities. In this context, it is difficult to maintain a continuous flow between these activities of the value chain. According to Sanofi (2017), 70% of the time of production of a vaccine is dedicated to activities performed by the quality control department including several hundreds of tests;

(iii) Manufacturing processes must be validated: It has a direct impact on the operations as the critical steps in the process are fixed. This means for example that changing batch size to speed up the process is not allowed unless a new validation is performed to demonstrate that the quality of the product is not impacted. Dividing the formulated volume of a biologic product by two require to demonstrate that the therapeutic effect and the stability of the product are not impacted. It is more

complex than just dividing by two the initially validated quantities of the product's components;

(iv) Outsourcing: when Pharmaceutical Supply Chain is broken because of outsourced activities, it may generate longer cycle time in the process of product supply. It has an impact on Inbound activities, operations and outbound activities. JIT in the context of outsourcing requires:

a. Accurate forecasts to be communicated to the third-party partners who must have sufficient raw materials available at the time of the order for performing the outsourced activities;

b. Efficient coordination in the entire process flow. For example, a delay in an upstream process performed by a third-party partner can impact significantly a downstream process performed by another partner.

4.5. Conclusion

This Part 4 was dedicated to the place of Lean in the Pharmaceutical Supply Chain and how it can improve it. Firstly, some elements that may explain the poor performance of the Supply Chain in the Pharmaceutical Industry were given. Then, practical cases were presented for illustrating the benefits of Lean: quick and significant good results that can be maintained as well if importance to an organic approach is given. Finally, an analysis was performed about how TPS elements are challenged by the Pharmaceutical Industry framework. The outcome of the analysis showed that JIT is a concept difficult to implement in the Pharmaceutical Industry.

5. Final conclusion

It may be difficult to understand why Pharmaceutical Industry which is a leader industry in terms of investment has its Supply Chain not performing well or at least not as expected. Quality issues, late delivery, product recall are problems that have not diminished over the years despite the experience gained in this industry. In Part 4, outsourcing, partners selection and the regulatory framework had been pointed out as the main causes of the poor performance of the Pharmaceutical Supply Chain. It is also necessary to quote other reasons that have not been explicitly said so far but which become now quite obvious based on the characteristics of the Pharmaceutical Industry and the case studies presented in the previous parts. These other reasons are also approached by Rees (2011), Staudacher & Bush (2014) and Basu et al. (2013).

Firstly, the cycle from drugs discovery until their first commercialization may take many years in which a lot of energy and money are spent in the hope of providing a drug with interesting therapeutics properties and that will generate a nice margin for the manufacturer. During this long period, there is however very low consideration given to the set-up of an efficient process from the raw materials to final delivery. The main reason is due to uncertainty regarding the marketing approval of the drug: development cycles stop immediately when objective evidences are given that the drug does not provide the expected therapeutics effect. Hence, this is very common to observe initiative of process improvement for drugs that are already on the market for years.

Secondly, and this is subsequent to the previous statement, once the drug has been authorized for commercialization, there is a need for a quick commercial Supply Chain to be set up. It would be not acceptable for the industry to waste more time in the large-scale commercialization of the drug when the long-awaited approval has been received from the competent Authorities. But drug manufacturing process is very complex as explained in Part 3. Wouldn't it deserve more attention to design a robust process with as few flaws as possible? Instead of that, the industry work with their historical partners or decide to integer new partners who can "do the job" at an attractive estimated cost.

And finally, the room for maneuver decreases significantly once all the processes are validated. Working with new partners or changing the design of a process may require validation stages if these changes are related to critical processes that may have an impact on the drug.

Figure 5.1 adapted from Basu et al. (2013) illustrates perfectly this comment. It would be more difficult to change the manufacturing processes after a product is launched. This statement can be extended to all the processes in the Pharmaceutical Supply Chain because problems related to quality, delivery or quantity can occur at each stages of the chain.

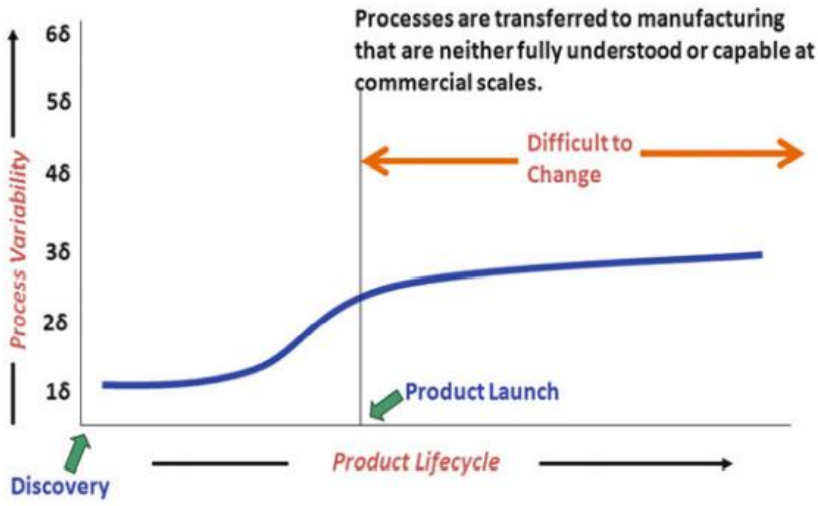


Figure 5.1 – The difficult change of manufacturing process (adapted with permission from Basu et al., 2018, p. 453)

The Lean approach is really complete in every sense. The company would achieve excellence in its operations by balancing the process flow, by eliminating as much as possible the waste generated in the chain and by improving the processes to make them as stable as possible. It is no coincidence that a company like Novo Nordisk which is a global and leading manufacturer in the Pharmaceutical Industry has decided to implement this philosophy to improve the performance indicators of its supply chain in the long term.

But turning completely to this philosophy requires disrupting certain well-established practices and it also requires the involvement of all the actors in the chain since for this to work, the whole chain must be Lean to a certain degree.

JIT which is a pillar of the Lean philosophy seems to be the most complicated core concept of Lean to implement in the Pharmaceutical Industry. The main systemic barriers to its implementation have been reviewed. A *romantic JIT* as described in the previous part is an ideal situation too complicated to set up in the Pharmaceutical Industry but this is not a reason for not having an effective inventory policy. Lean may be used to maintain an acceptable level

of inventory that does not put production at risk. The CGMPs require to evaluate the quality of the products before using them and this can only be demonstrated by tests to be carried out. So a pharma company could estimate through a Six Sigma approach the time necessary to carry out these tests and include this time in the calculation of the optimal orders quantities from a Lean point of view and not from an economical perspective only. A Six Sigma approach can be appropriate also to assess for example the capability of the suppliers to supply raw materials that are conform from a quality point of view. Indeed, from a Lean perspective, there is no added-value for the process to receive small quantities of materials on a regular basis if the rate of rejected materials is high. It is also important not to have excessive inventory as the shelf life of the products are calculated based on validation. Hence, excessive inventory increases the risk of stock obsolesce.

This approach requires a change in the mindset as some practices are very common in the Supply Chain in this industry like procurement practices not focused on supplier performance or maximization of batch sizes to minimize cost per unit (Rees, 2011).

The pull system that is very important in JIT approach has not been discussed deeply for the simple reason that most of the drugs must be produced based on forecasts. Due to the long manufacturing time, producing drugs when the users need them would lead immediately to drugs shortage situation on the market. So this is another difficulty: reducing as much as possible the inventory as per Lean while the products batches are scheduled based on forecasts can generate visions or dynamics that are very different from each other within an organization. For therapies such as transplants, production is made to meet a particular demand. Hence, due to its nature, this kind of process is not based on forecast and respect more the pull system. As it does not represent the most common process in the Pharmaceutical Industry, it has not been further discussed.

It is in the manufacturing process that Lean seems to have the biggest impact in the quest of improvement by its ability to simplify processes as far as it is allowed. But the analysis has highlighted another type of waste probably bigger than all the other waste: Lean in Pharmaceutical Industry may help to simplify processes that were made complicated in some instances during the design of the processes.

Therefore, this industry must integrate a minimum of considerations related to flows of products, deliveries, partners selection from the development phases and the first design of the

flows because changes may be difficult to implement once processes or suppliers are validated. Of course some companies may have processes less favorable for the implementation of Lean. For example a pharma company based in Europe that needs an ingredient that is only produced in China or India cannot design a Supply chain process that includes frequent deliveries from only local suppliers. The same observation applies to companies that use outsourcing because they do not have the capacity to perform all the Supply Chain steps internally. But when it is possible, pharma companies should favor, at equal quality, partnership with local actors able to deliver frequently good quality raw materials or services. Outsourcing is also a practice in the Pharmaceutical Industry that may cause troubles in the Supply Chain as it does not go into the sense of a simplification of the process. In a Lean approach, it is better to internalize processes for a better control and made them stable.

It is also necessary to remember that an important reason among the difficulties of implementing Lean in the supply chain in general is the poor lack of coordination, communication between partners and the lack of trust (c.f. Table 2.1). This kind of issues between two partners may even lead in worst case to troubles in the Supply Chain of others companies. For example, for the 2020 fiscal year, the Brussels Site of Catalent Belgium which is a CMO registered an increase of 111% of the inventory related to provision over the previous year (Banque Nationale de Belgique [nbb], 2020). The reason given in the 42th page of the annual accounts report available on nbb (2020) was related to a desire to increase the level of stock to ensure production activities because of possible impact of the Covid 19 pandemic on suppliers delivery activities. First, this kind of decision is based on uncertainty regarding the capacity of the suppliers to deliver which may be considered as a lack of trust. Then, it has also as consequence to increase the risk of inventory obsolescence. Finally, this decision may impact the Supply Chain of other companies: if the capacity of the suppliers is unchanged, such an increase in the quantities ordered may create out-of-stock situations at companies supplied by the same suppliers. This type of variability has negative impact on the Supply Chain activities. So trust and good communication between partners are needed for implementing Lean in the Supply Chain beyond the manufacturing activities.

To conclude, it can be stated that even if it cannot be implemented at every stages of the Supply Chain, Lean is an opportunity to realize that the Pharmaceutical Industry is an industry made in some cases of disorganized and interrupted flows with short-term cost-based procurement strategies. Hence the potential for improvement is important.

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7. Appendices

7.1. Appendix 1: Eudralex Volume 4 Chapter 5

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 13 August 2014

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 5: Production

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: Revision[a].

Reasons for changes: Changes have been made to sections 17 to 21, including adding a new section, to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment. Changes were also introduced in sections 27 to 30, including adding a new section, on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorisation holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Sections 35 and 36 are inserted to clarify and harmonise expectations of manufacturers regarding the testing of starting materials while section 71 introduces guidance on notification of restrictions in supply.

Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 20 has to be carried out:

[a] In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Furthermore, correction of the reference in footnote 2 took place.

- from 1 June 2015 onwards for any medicinal product newly introduced into shared manufacturing facilities;
- before 1 December 2015 for medicinal products already produced in a shared manufacturing facility producing only medicinal products for human use or producing both medicinal products for human use and veterinary medicinal products on 31 May 2015;
- before 1 June 2016 for veterinary medicinal products already produced in a shared manufacturing facility producing only veterinary medicinal products on 31 May 2015.

Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.

5.12 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean).

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control department when appropriate.

5.16 Access to production premises should be restricted to authorised personnel.

Prevention of cross-contamination in production

5.17 Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but, where justified, could be allowed where the measures to prevent cross-contamination with medicinal products described below and in Chapter 3 can be applied. The production and/or storage of technical poisons, such as pesticides (except where these are used for manufacture of medicinal products) and herbicides, should not be allowed in areas used for the manufacture and / or storage of medicinal products.

5.18 Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other starting materials, and products in process, from residues on equipment, and from operators' clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Products in which cross-contamination is likely to be most significant are those administered by injection and those given over a long time. However, contamination of all products poses a risk to patient safety dependent on the nature and extent of contamination.

5.19 Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross-contamination.

5.20 A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a

segregated, self contained production area within a multiproduct facility, where justified.

5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:

Technical Measures

i. Dedicated manufacturing facility (premises and equipment);

ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;

iii. Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning;

iv. Use of "closed systems" for processing and material/product transfer between equipment;

v. Use of physical barrier systems, including isolators, as containment measures;

vi. Controlled removal of dust close to source of the contaminant e.g. through localised extraction;

vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;

viii. Use of single use disposable technologies;

ix. Use of equipment designed for ease of cleaning;

x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;

xi. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

xii. Use of automatic clean in place systems of validated effectiveness;

xiii. For common general wash areas, separation of equipment washing, drying and storage areas.

Organisational Measures

i. Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;

ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;

iii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;

iv. Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;

v. Specific measures for waste handling, contaminated rinsing water and soiled gowning;

vi. Recording of spills, accidental events or deviations from procedures;

vii. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;

viii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

ix. Use of common general wash areas on a campaign basis;

x. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

5.22 Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.

Validation

5.23 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.24 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.25 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.

5.26 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Starting materials

5.27 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material.

5.28 The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification.

5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required:

Active substances[1]

Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the EEA based manufacturer or importer of the medicinal product.

Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorisation shall verify such compliance either by himself or through an entity acting on his behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk.

Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross-contamination from other materials on site. The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Any required corrective and preventive actions should be implemented.

Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.

Excipients

Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the European Commission 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use'.

5.30 For each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order, the supplier's labels and approved manufacturer and supplier information maintained by the medicinal product manufacturer. The receiving checks on each delivery should be documented.

[1] Specific requirements apply to the importation of active substances to be used in the manufacture of medicinal products for human use in article 46b of Directive 2001/83/EC.

5.31 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.32 Starting materials in the storage area should be appropriately labelled (see section 13). Labels should bear at least the following information:

i. The designated name of the product and the internal code reference where applicable;

ii. A batch number given at receipt;

iii. Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);

iv. Where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

5.33 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6).

5.34 Only starting materials which have been released by the Quality Control department and which are within their retest period should be used.

5.35 Manufacturers of finished products are responsible for any testing of starting materials[2] as described in the marketing authorisation dossier. They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing[3] of each batch according to Annex 8.

5.36 The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled:

i. Special attention should be paid to the distribution controls (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material;

ii. The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the marketing authorisation dossier;

iii. The certificate of analysis provided by the starting material manufacturer/supplier should be signed by a designated person with appropriate qualifications and experience. The signature assures that each batch has been checked for compliance with the agreed product specification unless this assurance is provided separately;

iv. The medicinal product manufacturer should have appropriate experience in dealing with the starting material manufacturer (including experience via a supplier)

[2] A similar approach should apply to packaging materials as stated in section 5.45.
[3] Identity testing of starting materials should be performed according to the methods and the specifications of the relevant marketing authorisation dossier.

including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered;

v. The medicinal product manufacturer should also perform (or via a separately approved contract laboratory) a full analysis at appropriate intervals based on risk and compare the results with the material manufacturer or supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier should be discontinued until these measures are completed.

5.37 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.38 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.39 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

5.40 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.41 Intermediate and bulk products should be kept under appropriate conditions.

5.42 Critical processes should be validated (see "Validation" in this Chapter).

5.43 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.44 Any significant deviation from the expected yield should be recorded and investigated.

Packaging materials

5.45 The selection, qualification, approval and maintenance of suppliers of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.46 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.47 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.48 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging operations

5.49 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.50 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

5.51 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.52 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.53 Containers for filling should be clean before filling. Attention should be given to avoid and remove any contaminants such as glass fragments and metal particles.

5.54 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

5.55 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.56 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

5.57 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.58 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.59 On-line control of the product during packaging should include at least checking the following:

i. General appearance of the packages;

ii. Whether the packages are complete;

iii. Whether the correct products and packaging materials are used;

iv. Whether any over-printing is correct;

v. Correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.60 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

5.61 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.62 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock.

Finished products

5.63 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.64 The evaluation of finished products and documentation which is necessary before release of product for sale is described in Chapter 6 (Quality Control).

5.65 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

5.66 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.

5.67 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

5.68 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.69 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.70 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

Product shortage due to manufacturing constraints

5.71 The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations4.

[4] Articles 23a and 81 of Directive 2001/83/EC

7.2. Appendix 2: Eudralex Volume 4 Chapter 7

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and Products
Medicinal Products - Quality, safety and efficacy

Brussels,
SANCO/AM/sl/ddg1.d.6(2012)860362

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4

EU Guidelines for

Good Manufacturing Practice for

Medicinal Products for Human and Veterinary Use

Chapter 7
Outsourced Activities

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: revision 1

Reasons for changes: In view of the ICH Q10 guideline on the Pharmaceutical Quality System, Chapter 7 of the GMP Guide has been revised in order to provide updated guidance on outsourced GMP regulated activities beyond the current scope of contract manufacture and analysis operations. The title of the Chapter has been changed to reflect this.

Deadline for coming into operation: 31 January 2013

Principle

Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of Contract Acceptors and Contract Givers to consumers; this is governed by other provisions of Community and national law.

General

7.1 There should be a written Contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.

7.3 Where the marketing authorization holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

The Contract Giver

7.4 The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:

7.5 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the Contract that the principles and guidelines of GMP as interpreted in this Guide are followed.

7.6 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is

fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

7.7 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

7.8 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure, either by himself, or based on the confirmation of the Contract Acceptor's Qualified Person, that all products and materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation.

The Contract Acceptor

7.9 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.

7.10 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him are suitable for their intended purpose.

7.11 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him under the Contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.

7.12 The Contract Acceptor should not make unauthorized changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.

7.13 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

The Contract

7.14 A Contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the Contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties.

7.15 The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials,

undertaking production and quality controls (including in-process controls, sampling and analysis).

7.16 All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

7.17 The Contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractors

7.3. Appendix 3: Eudralex Volume 4 Annex 15

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EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Medicinal Products – Quality, Safety and Efficacy

Brussels, 30 March 2015

EudraLex

Volume 4

EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Annex 15: Qualification and Validation

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: Revision

Reasons for changes: Since Annex 15 was published in 2001 the manufacturing and regulatory environment has changed significantly and an update is required to this Annex to reflect this changed environment. This revision to Annex 15 takes into account changes to other sections of the EudraLex, Volume 4, Part I, relationship to Part II, Annex 11, ICH Q8, Q9, Q10 and Q11, QWP guidance on process validation, and changes in manufacturing technology.

Deadline for coming into operation: 1 October 2015

Principle

This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to EudraLex, Volume 4, Part II. It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should also be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account.

General

A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. Retrospective validation is no longer considered an acceptable approach. Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.

1. ORGANISING AND PLANNING FOR QUALIFICATION AND VALIDATION

1.1. All qualification and validation activities should be planned and take the life cycle of facilities, equipment, utilities, process and product into consideration.

1.2. Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures.

1.3. Qualification/validation personnel should report as defined in the pharmaceutical quality system although this may not necessarily be to a quality management or a quality assurance function. However, there should be appropriate quality oversight over the whole validation life cycle.

1.4. The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.

1.5. The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following:

i. Qualification and Validation policy;

ii. The organisational structure including roles and responsibilities for qualification and validation activities;

iii. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;

iv. Change control and deviation management for qualification and validation;

v. Guidance on developing acceptance criteria;

vi. References to existing documents;

vii. The qualification and validation strategy, including requalification, where applicable.

1.6. For large and complex projects, planning takes on added importance and separate validation plans may enhance clarity

1.7. A quality risk management approach should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the project phase or during commercial production, the risk assessments should be repeated, as required. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

1.8. Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.

2. DOCUMENTATION, INCLUDING VMP

2.1. Good documentation practices are important to support knowledge management throughout the product lifecycle.

2.2. All documents generated during qualification and validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.

2.3. The inter-relationship between documents in complex validation projects should be clearly defined.

2.4. Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.

2.5. Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).

2.6. Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

2.7. Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.

2.8. Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report

2.9. The review and conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.

2.10. A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

3. QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES, UTILITIES AND SYSTEMS.

3.1. Qualification activities should consider all stages from initial development of the user requirements specification through to the end of use of the equipment, facility, utility or system. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:

User requirements specification (URS)

3.2. The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.

Design qualification (DQ)

3.3. The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.

Factory acceptance testing (FAT) /Site acceptance testing (SAT)

3.4. Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.

3.5. Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable.

3.6. Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation.

3.7. FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

Installation qualification (IQ)

3.8. IQ should be performed on equipment, facilities, utilities, or systems.

3.9. IQ should include, but is not limited to the following:

i. Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;

ii. Verification of the correct installation against pre-defined criteria;

iii. Collection and collation of supplier operating and working instructions and maintenance requirements;

iv. Calibration of instrumentation;

v. Verification of the materials of construction.

Operational qualification (OQ)

3.10. OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).

3.11. OQ should include but is not limited to the following:

i. Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;

ii. Tests to confirm upper and lower operating limits, and /or "worst case" conditions.

3.12. The completion of a successful OQ should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements.

Performance qualification (PQ)

3.13. PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.

3.14. PQ should include, but is not limited to the following:

i. Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified;

ii. Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

4. RE-QUALIFICATION

4.1. Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

4.2. Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.

5. PROCESS VALIDATION

General

5.1. The requirements and principles outlined in this section are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, site transfers and ongoing process verification. It is implicit in this annex that a robust product development process is in place to enable successful process validation.

5.2. Section 5 should be used in conjunction with the current EMA guideline on Process Validation.

5.2.1. The guideline on Process Validation is intended to provide guidance on the information and data to be provided in the regulatory submission only. However GMP requirements for process validation continue throughout the lifecycle of the process

5.2.2. This approach should be applied to link product and process development. It will ensure validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

5.3. Manufacturing processes may be developed using a traditional approach or a continuous verification approach. However, irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes using the traditional approach should undergo a prospective validation programme, wherever possible, prior to certification of the product. Retrospective validation is no longer an acceptable approach.

5.4. Process validation of new products should cover all intended marketed strengths and sites of manufacture. Bracketing could be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme.

5.5. For process validation of products which are transferred from one site to another or within the same site, the number of validation batches could be reduced by the use of a bracketing approach. However, existing product knowledge, including the content of the previous validation, should be available. Different strengths, batch sizes and pack sizes/container types may also use a bracketing approach, if justified.

5.6. For the site transfer of legacy products, the manufacturing process and controls must comply with the marketing authorisation and meet current standards for

marketing authorisation for that product type. If necessary, variations to the marketing authorisation should be submitted.

5.7. Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.

5.8. Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified or specified in other sections of EudraLex, Volume 4.

5.9. Equipment, facilities, utilities and systems used for process validation should be qualified. Test methods should be validated for their intended use.

5.10. For all products irrespective of the approach used, process knowledge from development studies or other sources should be accessible to the manufacturing site, unless otherwise justified, and be the basis for validation activities.

5.11. For process validation batches, production, development, or other site transfer personnel may be involved. Batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding.

5.12. The suppliers of critical starting and packaging materials should be qualified prior to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented.

5.13. It is especially important that the underlying process knowledge for the design space justification (if used) and for development of any mathematical models (if used) to confirm a process control strategy should be available.

5.14. Where validation batches are released to the market, this should be pre-defined. The conditions under which they are produced should fully comply with GMP, with the validation acceptance criteria, with any continuous process verification criteria (if used) and with the marketing authorisation or clinical trial authorisation.

5.15. For the process validation of investigational medicinal products (IMP), please refer to Annex 13.

Concurrent validation

5.16. In exceptional circumstances, where there is a strong benefit-risk ratio for the patient, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, documented in the VMP for visibility and approved by authorised personnel.

5.17. Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Qualified Person prior to certification of the batch.

Traditional process validation

5.18. In the traditional approach, a number of batches of the finished product are manufactured under routine conditions to confirm reproducibility.

5.19. The number of batches manufactured and the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

5.20. Without prejudice to 5.19, it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise.

5.21. A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.

5.22. Process validation protocols should include, but are not limited to the following:

i. A short description of the process and a reference to the respective Master Batch Record;

ii. Functions and responsibilities;

iii. Summary of the CQAs to be investigated;

iv. Summary of CPPs and their associated limits;

v. Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;

vi. List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;

vii. List of analytical methods and method validation, as appropriate.

viii. Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;

ix. Additional testing to be carried out with acceptance criteria;

x. Sampling plan and the rationale behind it;

xi. Methods for recording and evaluating results;

xii. Process for release and certification of batches (if applicable).

Continuous process verification

5.23. For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.

5.24. The method by which the process will be verified should be defined. There should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

5.25. The general principles laid down in 5.1 – 5.14 above still apply.

Hybrid approach

5.26. A hybrid of the traditional approach and continuous process verification could be used where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data.

5.27. This approach may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.

Ongoing Process Verification during Lifecycle

5.28. Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.

5.29. Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

5.30. The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.

5.31. Ongoing process verification should be conducted under an approved protocol or equivalent documents and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.

5.32. Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed.

6. VERIFICATION OF TRANSPORTATION

6.1. Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorisation, the approved label, product specification file or as justified by the manufacturer.

6.2. It is recognised that verification of transportation may be challenging due to the variable factors involved however, transportation routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport

6.3. A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.

6.4. Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the product may be subjected should be performed, unless otherwise justified.

7. VALIDATION OF PACKAGING

7.1. Variation in equipment processing parameters especially during primary packaging may have a significant impact on the integrity and correct functioning of the pack, e.g. blister strips, sachets and sterile components, therefore primary and secondary packaging equipment for finished and bulk products should be qualified.

7.2. Qualification of the equipment used for primary packing should be carried out at the minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure or for any other factors.

8. QUALIFICATION OF UTILITIES

8.1. The quality of steam, water, air, other gases etc. should be confirmed following installation using the qualification steps described in section 3 above.

8.2. The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.

8.3. A risk assessment should be carried out where there may be direct contact with the product, e.g. heating, ventilation and air-conditioning (HVAC) systems, or indirect contact such as through heat exchangers to mitigate any risks of failure.

9. VALIDATION OF TEST METHODS

9.1. All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit, where necessary, as defined in Chapter 6 of the EudraLex, Volume 4, Part I.

9.2. Where microbial testing of product is carried out, the method should be validated to confirm that the product does not influence the recovery of microorganisms.

9.3. Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising agents do not influence the recovery of microorganisms.

10. CLEANING VALIDATION

10.1. Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.

10.2. A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.

10.3. It is recognised that a cleaning validation programme may take some time to complete and validation with verification after each batch may be required for some products, e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

10.4. Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.

10.5. For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.

10.6. Limits for the carryover of product residues should be based on a toxicological evaluation[1]. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria

[1] See EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

should consider the potential cumulative effect of multiple items of equipment in the process equipment train.

10.6.1. Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.

10.6.2. If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.

10.7. The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.

10.8. The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process.

10.9. Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.

10.10. Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity and potency.

10.11. Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.

10.12. Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

10.13. The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.

10.14. Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures should be used for each product as indicated in chapters 3 and 5 of EudraLex, Volume 4, Part I.

10.15. Where manual cleaning of equipment is performed, it is especially important that the effectiveness of the manual process should be confirmed at a justified frequency.

11. CHANGE CONTROL

11.1. The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.

11.2. Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, process, equipment, premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility.

11.3. Where design space is used, the impact on changes to the design space should be considered against the registered design space within the marketing authorisation and the need for any regulatory actions assessed.

11.4. Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.

11.5. Changes should be authorised and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.

11.6. Supporting data, e.g. copies of documents, should be reviewed to confirm that the impact of the change has been demonstrated prior to final approval.

11.7. Following implementation, and, where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.

12. GLOSSARY

Definitions of terms relating to qualification and validation which are not given in other sections of the current EudraLex, Volume 4, are given below.

Bracketing approach. A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors, e.g. strength, batch size and/or pack size, are tested during process validation. The design assumes that validation of any intermediate levels is represented by validation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, e.g. for a tablet range made with different compression weights of a similar basic granulation or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells. Bracketing can be applied to different container sizes or different fills in the same container closure system.

Change Control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.

Cleaning Validation. Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.

Cleaning verification. The gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum allowable carryover level.

Concurrent Validation. Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches.

Continuous process verification. An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

Control Strategy. A planned set of controls derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control. (ICH Q10)

Critical process parameter (CPP). A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

Critical quality attribute (CQA). A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality. (ICH Q8)

Design qualification (DQ). The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Design Space. The multidimensional combination and interaction of input variables, e.g. material attributes, and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change.

Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

Installation Qualification (IQ). The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Knowledge management. A systematic approach to acquire, analyse, store and disseminate information. (ICH Q10)

Lifecycle. All phases in the life of a product, equipment or facility from initial development or use through to discontinuation of use.

Ongoing Process Verification (also known as continued process verification). Documented evidence that the process remains in a state of control during commercial manufacture.

Operational Qualification (OQ). The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ). The documented verification that systems and equipment can perform effectively and reproducibly based on the approved process method and product specification.

Process Validation. The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Product realisation. Achievement of a product with the quality attributes to meet the needs of patients, health care professionals and regulatory authorities and internal customer requirements. (ICH Q10)

Prospective Validation. Validation carried out before routine production of products intended for sale.

Quality by design. A systematic approach that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management.

Quality risk management. A systematic process for the assessment, control, communication and review of risks to quality across the lifecycle. (ICH Q9)

Simulated agents. A material that closely approximates the physical and, where practical, the chemical characteristics, e.g. viscosity, particle size, pH etc., of the product under validation.

State of control. A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality.

Traditional approach. A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.

Worst Case. A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

User requirements Specification (URS). The set of owner, user and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system.

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