Improvement of quality of medications through implementing the six sigma methodology

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The increased competition in the global pharmaceutical market and the necessity to reach higher levels of quality of the pharmaceutical products force the manufacturers to seek and adopt more effective and reliable quality management methods and techniques which allow them to introduce products with the highest possible quality level and reduced quality costs while maintaining conformance to the pharmaceutical GMPs, technical and legislative requirements.

One of the popular modern quality management methodologies is Six Sigma, which proved its high ability to increase business profits and competitiveness within more than 30 years of implementation in manufacturing and service sectors. Recently, Six Sigma methodology has been adopted by global pharmaceutical companies such as Baxter, Eli Lilly, Johnson & Johnson and Novartis and obtained considerable benefits from its abilities.

This research aims at investigating the possibility to improve the quality of medications through implementing the six sigma methodology, and to find out what benefits a pharmaceutical company can get through the implementation of this methodology. A case study was conducted in a pharmaceutical company in Syria (Orient-Pharma) in order to examine the effectiveness and advantages of Six Sigma methodology.

For this purpose, a quality improvement project was conducted using DMAIC roadmap to enhance the quality for one of the main products of the company. The obtained results of DMAIC project showed an enhanced process capability, an enhanced process Sigma level, decreased variability in the process outputs, as a result the quality of the medication had been enhanced sufficiently. As a conclusion, considerable benefits can be obtained through implementing Six Sigma methodology in the pharmaceutical industry to improve the medications quality and the production processes as well.

Keywords: quality improvement, six sigma methodology, pharmaceutical industry, DMAIC methodology.

Introduction

Six Sigma methodology was developed at Motorola company in 1987 as a way to achieve business excellence. Many researchers attempted to provide a comprehensive description of Six Sigma concept. Six Sigma is a rigorous and high efficiency application of the proved quality principles and techniques. It combines elements from the scientific works of quality management pioneers and different methodologies, and aims to reach a level of performance which does not contain any defects [1-4].

The term «Sigma» is symbolized by the Greek letter σ and used by statisticians to measure the variability in process outputs, so the company's performance is measured by the Sigma level of its processes. Historically, companies accepted performance level at three or four sigma standard in spite of the fact that the processes at that performance level produced 6200-67000 defects per million opportunities (DPMO). However, the standard six sigma (equal to 3.4 DPMO) represents a response to the growing requirements of the customers and the growing complexity of manufacturing processes and new products [2, 18]. Six Sigma is defined as a strategy to improve business performance of an organization as a whole. It is characterized by a high degree of organization and discipline, and a strong focus on the customers and the efforts towards improving organization's profitability. Six Sigma uses effective statistical methods and is based on quality principles used to improve processes and products through a framework known as DMAIC that consists of five consecutive phases (Define, Measure, Analyze, Improve, Control) [3]. Six Sigma also is a systematic data-driven methodology aimed at solving chronic problems, which business sectors encounter. It provides an excellent framework to manage improvement projects; and applies a lot of statistical and non-statistical tools in a manner provides the best solutions of the investigated problems [4]. Six Sigma is a much-disciplined methodology that relies on statistics to eliminate the defects in products and processes, and depends on the full involvement of the company's personnel [5].

Methodology

This research aims at implementing Six Sigma methodology in a Syrian Pharmaceutical Company (ORIENT PHARMA) to improve the perceived quality

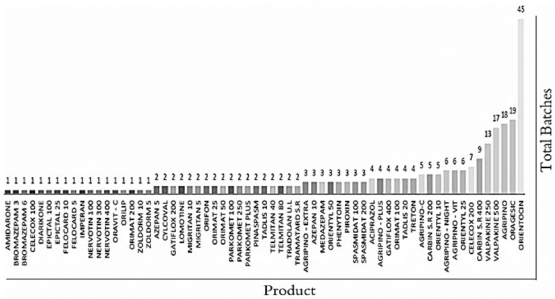

Fig. 1. Annual production for all kinds of products

Table 1

Project Charter

Problem statement	The analytical data (supplied by the quality control lab. In the considered company) demonstrated a significant variability in the concentration of API in the finished product Orientocin – Tablets (the standard deviation value near 3500). This problem decreases the homogeneity of the produced unites and affects the quality and effectiveness of the medicine negatively
Improvement goal	To decrease the variability in the concentration of API in the finished product Orientocin – Tablets, to enhance process capability and to sigma level to the higher possible value
Project scope and limitation	The project covers the first two stages of the manufacturing process of the product Stage 1 'Formula preparation' and Stage 2 'Tablets formation'
Key performance indicators	Process capability index Ppk , Process Mean , Standard deviation Std . D , Sigma level
Project team	A cross-functional team includes members from production department, quality control laboratories, quality assurance
Critical-to-quality characteristic	API concentration in the finished product , each tablet should contain (774900 IU) ±10%

level of one of the main products manufactured by this company. The project goals include enhancement of process capability and decrease of its variability in order to achieve a higher Sigma level while keeping the full fulfillment of GMPs and ISO 9001 requirements and other regulations [12-15]. To achieve this purpose, a DMAIC quality improvement project was designed in collaboration between the researchers and the interested departments in the company.

Table 2

Data set (before improvement)

Concentration of Spiramycine in each single tablet				Sample
814105,08	712326,35	786282,70	748983,36	1
751732,28	765466,22	738141,52	807598,64	2
820743,70	826338,23	784198,84	744493,58	3
729955,8	791388,32	782783,59	783988,56	4
726349,67	776623,88	755035,34	752702,08	5
778235,43	778985,67	767702,03	761741,15	6
745692,22	810163,70	746575,48	709386,50	7
712908,36	759402,64	777966,39	751653,11	8
748464,41	785748,68	823716,94	767159,78	9
782676,26	790873,70	736955,62	837044,65	10
782816,40	775379,26	729363,98	780268,57	11
783158,95	806399,59	776008,99	698562,66	12
731918,01	796241,47	809655,57	781179,10	13
767534,60	771724,85	758325,92	764158,61	14
766810,77	770208,46	765299,34	790165,9	15
765209,28	770734,25	756776,40	745395,2	16
722869,20	800763,52	743832,97	773001,15	17
774612,91	770083,07	785735,64	773984,201	18
803735,24	818007,63	776686,56	744419,41	19
762737,43	778985,67	767702,03	761741,15	20
776688,22	779167,70	769822,48	748131,50	21
748464,41	785748,63	777222,94	743912,78	22
773443,47	766404,75	787426,88	715232,71	23
778235,43	778985,67	752204,03	707498,15	24

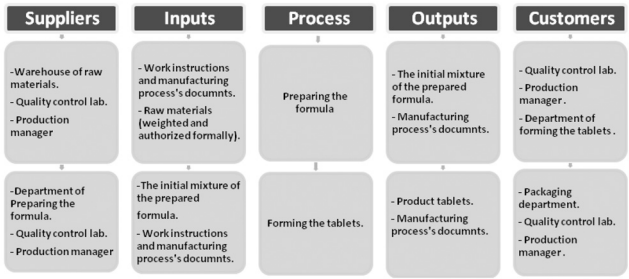

Fig. 2. High process level map (SIPOC) for the studied product

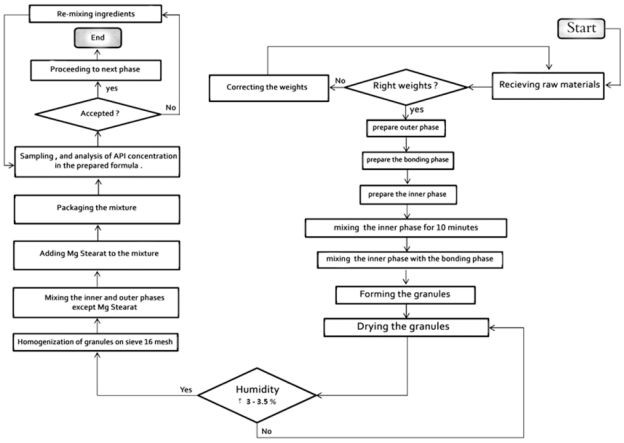

Fig. 3. Flow chart of the process at the stage «Formula preparation»

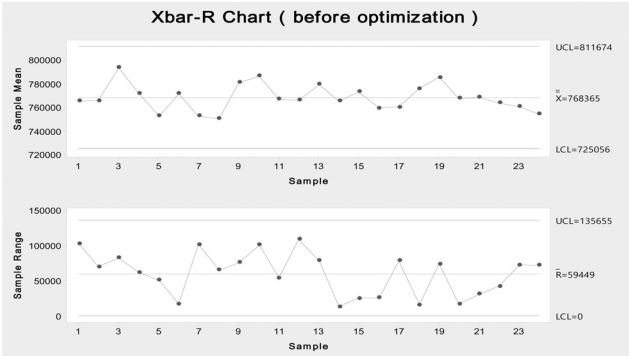

Fig. 4. Xbar-R control chart (before improvement) using software (Minitabv15)

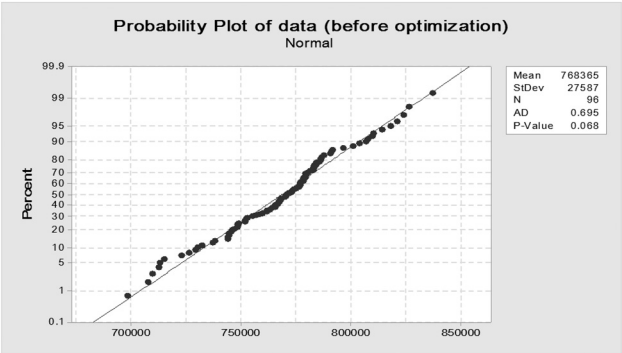

Fig. 5. Probability test (before improvement) using software (Minitabv15)

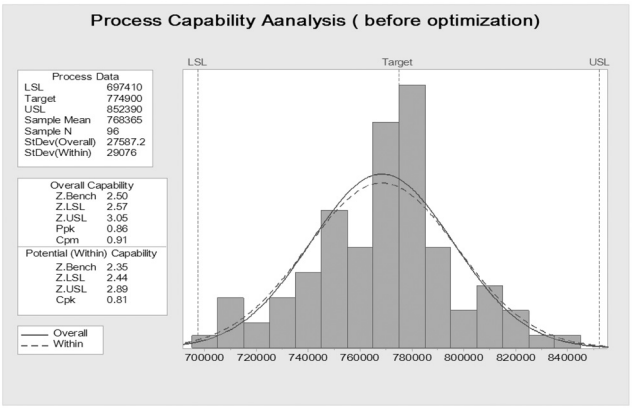

Fig. 6. Process Capability Analysis before improvement, using software (Minitabv15)

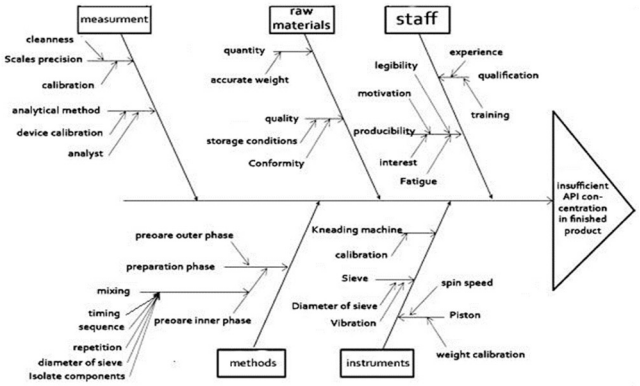

Fig. 7. Cause-and-effect diagram

1st. The define phase.

To determine the main product, the annual production records were reviewed as shown in fig. 1.

It's noticeable that the product «Orientocin – Tablets» is the main product of the company (45 batches per year). «Orientocin – Tablets» is a medicine used to treat gingivitis; its main API (active pharmaceutical ingredient) is «Spiramycine». The team developed the project charter as shown in table 1.

The investigated stages of the process are illustrated in the following SIPOC diagram (fig. 2).

2nd. The measurement phase.

To establish a general understanding of the investigated process (Preparing the formula), the project team developed a Flow chart diagram as shown in fig. 3.

Sampling and Measurement plan:

- Investigated characteristic: API concentration in product tablets.
- Measurement procedure: the formal analytical method used in quality control lab in the company.
- Measurement techniques: Molecular absorption spectroscopy.
- Sampling: the samples were collected from the outputs of forming phase (tableting) as follows:
- Sample size: n = 4 tablets.
- Frequency: 1 sample each 5 minutes.
- Collected samples: 24.
- Sampling responsibility: process operator.

Data set:

According to the Sampling and Measurement plan, the data set had been collected (see table 2).

Checking process stability:

By using software (Minitabv15) the project team created an Xbar-R control chart as shown in fig. 4. All points fall between UCL and LCL. No patterns were observed, so the process was under statistical control.

Table 3

Data set (after improvement)

Concentration of Spiramycine in each single tablet				Sample
785748,61	770842,58	763853,35	791172,95	1
795047,41	774854,42	773079,26	785121,75	2
791553,31	773069,07	761008,78	755766,25	3
738479,71	768514,85	778774,51	755865,85	4
764972,63	784198,81	771215,23	753096,61	5
780767,82	729770,36	747003,61	764048,74	6
759842,83	766477,22	746228,71	768585,61	7
776348,34	774125,11	742354,21	784198,83	8
758072,35	805896,31	756644,191	754243,98	9
753202,81	753977,71	784198,81	756568,03	10
770900,84	794272,51	777224,71	779549,41	11
764972,62	763276,51	748553,41	791841,61	12
764972,63	801246,61	770250,62	760845,62	13
755402,84	800471,71	749328,31	785121,71	14
765821,34	772863,94	799696,82	769741,98	15
757223,63	760176,91	770250,61	763276,51	16
768700,81	750979,22	784198,82	760836,61	17
752648,96	758231,80	776682,27	764317,01	18
788437,45	763093,58	743904,01	773301,64	19
763151,86	788073,31	773079,26	785121,71	20
763151,84	789623,11	764593,83	777372,75	21
776348,34	761729,27	772575,31	767733,68	22
759842,83	769475,71	755711,86	760836,66	23
752648,91	776449,81	761998,99	780324,31	24

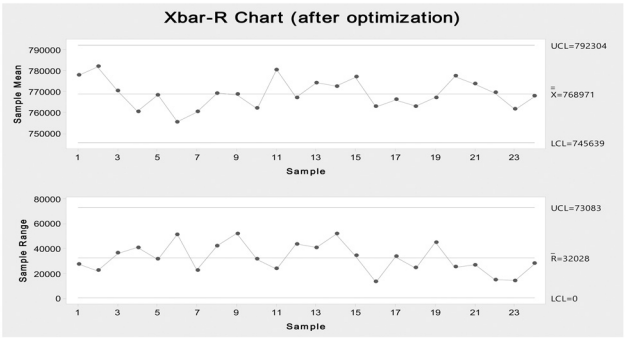

Fig. 8. Xbar-R control chart (after improvement)

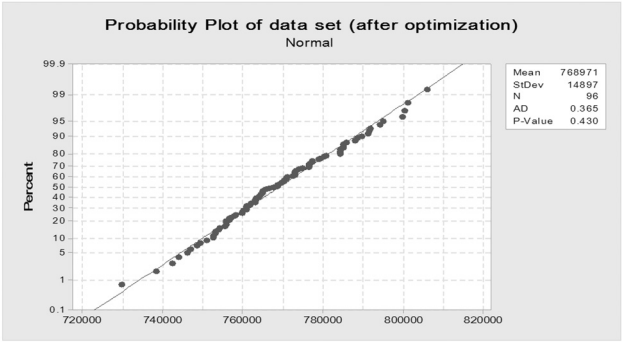

Fig. 9. Process Capability Analysis (after improvement) using software (Minitabv15)

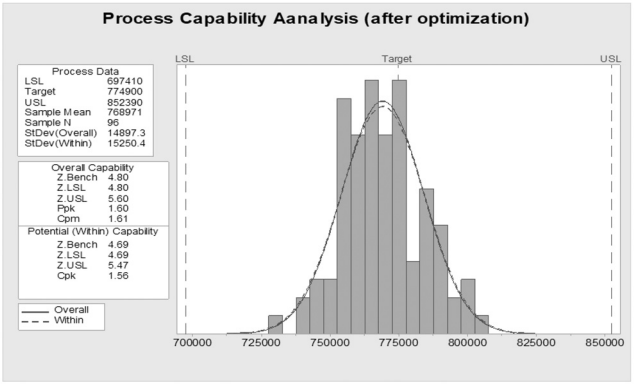

Fig. 10. Process Capability Analysis (after improvement) using software (Minitab v15)

3rd. The analysis phase.

To examine the normality of the data set, probability test was conducted as shown in (fig. 5).

The test showed that the data follows the normal distribution law and it is reliable to conduct a Process Capability Analysis: fig. 6.

The project team conducted a brainstorming to determine the possible causes of the studied problem and created Cause-and-effect diagram as shown in fig. 7.

The project team determined through brainstorming and technical expertise that the main causes affecting the investigated problem are:

- Method of isolation inner phase components.
- Repetition of mixing the inner phase components of the product.
- Sequence of mixing inner phase components.
- Diameter of used sieves.

4th. Improvement phase.

New process activities were established considering the determined causes in the analysis phase; in addition, a new flow chart was prepared for the sub process (preparing of inner phase) concerning the mechanism of preparing the inner phase of the studied product. The developed solution was applied on one batch. New measurements were conducted to collect the data set (table 3, fig. 8-10).

The achieved results showed that Process capability index Ppk has been increased from 0.86 to1.60. Sigma level of the investigated process has been raised from 2.50 to 4.80. Process variability decreased about 50% (table 4).

5th. The Control phase.

In this phase, the project team accomplished the following activities:

- Validating the new process.
- Updating process documents.
- Training process operators on the new operation instructions.
- Controlling the process through the established Xbar-R chart to keep the process under statistical control.
- Updating the performance indices of the process to maintain the received enhancements.

The conclusions

The obtained results of implementing Six Sigma methodology showed an enhanced process capability, an enhanced process Sigma level, decreased variability in the process outputs, as a result the quality of the medication had been enhanced sufficiently. As a conclusion, considerable benefits can be obtained through implementing Six Sigma methodology in the pharmaceutical industry to improve the medications quality and the production processes as well.

Table 4

Comparison between KPI before and after improvement

Process Mean (IU)	Sigma level	Ppk	St. D	
768365	2,50	0,86	27587,2	Before
768971	4,80	1,60	14897,3	After

References

1. D. V. Antipov, Yu. G. Gushyan, Yu. S. Klochkov, Yu. S. Eliseev, A. N. Chekmarev. Evaluation of the functioning of the system of logistics management of the quality of the technological process//Izvestiya Samarskogoauchnogo center of the Russian Academy of Sciences. 2016. Vol. 18. No. 4-1. P. 45-48.
2. K. B. Farris, D. M. Kirking (1993). Assessing the quality of pharmaceutical care II. Application of concepts of quality assessment from medical care//Annals of Pharmacotherapy, 27(2), 215-223.
3. I. H. T. Guideline (2005). Pharmaceutical development Q8.
4. I. H. T. Guideline (2008). Pharmaceutical quality system Q10.
5. I. H. T. Guideline (2005). Quality risk management Q9.
6. Y. S. Klochkov, A. D. Volgina, A. A. Karsuntseva, T. S. Selezneva, A. Yu. Gazizulina. Development of a product certification model based on QFD//Vector of the science of Togliatti State University. 2013. No. 4 (26). P. 111-113.
7. International Organization for Standardization (2015). Quality management systems — Fundamentals and vocabulary.
8. X. Y. Lawrence (2008). Pharmaceutical quality by design: product and process development, understanding, and control//Pharmaceutical research, 25 (4), 781-791.
9. T. Lofthouse (1999). The Taguchi loss function//Work Study, 48(6), 218-223.
10. M. M. A. Potdar (2006). Pharmaceutical quality assurance. Pragati Books Pvt. Ltd.
11. A. Rostami-Hodjegan, P. R. Jackson, G. T. Tucker (1994). Sensitivity of indirect metrics for assessing «rate» in bioequivalence studies — moving the «goalposts» or changing the «game»//Journal of pharmaceutical sciences, 83(11), 1554-1557.
12. R. K. Roy (2010). A primer on the Taguchi method. Society of Manufacturing Engineers.
13. G. Taguchi (1986). Introduction to quality engineering: designing quality into products and processes (No. 658.562 T3).
14. G. Taguchi (1993). Methods for Evaluating Quality. ASME press.
15. G. Taguchi, S. Chowdhury, Y. Wu (2005). Taguchi's quality engineering handbook (Vol. 1736). Hoboken, NJ: John Wiley & Sons.
16. J. F. van Leeuwen, M. J. Nauta, D. De Kaste, Y. M. C. F. Odekerken-Rombouts, M. T. Oldenhof, M. J. Vredenbregt, D. M. Barends (2009). Risk analysis by FMEA as an element of analytical validation//Journal of pharmaceutical and biomedical analysis, 50(5), 1085-1087.
17. L. X. Yu, A. Raw, R. Lionberger, R. Rajagopalan, L. M. Lee, F. Holcombe, R. Adams (2007). US FDA question-based review for generic drugs: A new pharmaceutical quality assessment system//Journal of Generic Medicines, 4 (4), 239-246.

Улучшение качества лекарственных средств через осуществление методологии «шесть сигм»

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Это исследование нацелено на изучение возможности улучшения качества лекарств путем внедрения методологии «шесть сигм» и выяснения преимуществ фармацевтической компании в реализации этой методологии. Примерное исследование было проведено в фармацевтической компании в Сирии (Orient-Pharma) для изучения эффективности и преимуществ методологии «шесть сигм».

С этой целью был проведен проект улучшения качества с использованием дорожной карты DMAIC для повышения качества одной из основных продуктов компании. Полученные результаты проекта DMAIC показали улучшенные возможности процесса, улучшенный уровень Sigma процесса, снижение вариабельности результатов процесса, в результате качество лекарственного средства было значительно улучшено. В качестве вывода можно извлечь значительные выгоды благодаря внедрению методологии Six Sigma в фармацевтической промышленности для улучшения качества лекарств и производственных процессов.

Ключевые слова: улучшение качества, методология «шесть сигм», фармацевтическая промышленность, методология DMAIC.