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The Application of Six Sigma in Process Control of Raw Water Quality on Pharmaceutical Industry at Indonesia

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Abstract

Quality is one of the important keys in the pharmaceutical industry in order to face and win the competition. Instability in the water treatment process causes the water quality does not comply with quality standards. This study aimed to evaluate the water treatment process in the pharmaceutical industry, to investigate the cause of the case out of specification (OOS) and propose improvements through application of six sigma method. The object of this research done on some parameters of water generated in the water treatment process, such as pH, conductivity and total plate count. Stages of procedures performed in this study included analysis of data normality, control chart analysis and determine the process capability. Minitab software also used to assist in the calculation and analysis. The results showed the improvement process provide a significant change with the increase in the average an index of Capability Process around 1.07 and decrease the possibility of producing a defective system of about 712 ppm. Furthermore, the study also indicates an increase in the sigma level from 2.30 into 4.69.

Keywords: Quality, WTP, Six Sigma, DMAIC, Pharmaceutical industry

INTRODUCTION

One of the materials most widely used in the pharmaceutical industry is water [1]. For example, raw material production, supporting the production process, cleaning apparatus and quality control [2]; [3]. Furthermore, water also is the main priority in terms of quality in the pharmaceutical industry [4]. This is due to the chemical properties of the water that is capable of being solvent, absorbing and retaining a variety of different compounds [1]. The water sources used in the pharmaceutical industry in Indonesia may vary widely, such as ground water and water provided by the Regional Water Company.

The water must pass through water treatment systems and must meet various high standards such as physical, chemical and microbiological. This is to assure that no contamination of equipment used and products. Several water quality parameters should be tested regularly and fit the definition of a good quality, for example, conductivity, the total organic carbon (TOC), nitrates, heavy metals, pH and microbiology [5]. Additionally, WHO underlines the water quality control is a top priority in every process of the pharmaceutical industry [1]. Moreover, the research conducted by Rivero et al. underlines the significant influence of pharmaceutical water systems in the manufacturing process to the final product quality [6]. This is due to the water quality of the pharmaceuticals used as raw materials for products in the formulation and as a cleaning media. Therefore, strict monitoring of the chemical and microbiological specifications are always based on international standards such as United Stated Pharmacopeia (USP) and the European Pharmacopeia (EP).

Raw water is referred to in this study is purified water or deionized water (DIW), which has passed through a UV filter 0,22µm. DIW generated should always be controlled via the looping system thus the quality is still of the standard, especially if a new use for more than 24 hours since produced. Looping in the system, purified water will be screened to keep it running, not stagnant in place that can lead to the growth of microorganisms.

Raw water is purified water created through a distillation process, the process of ion exchange, reverse osmosis or other suitable processes. The source of water used in the process must comply with regulations on drinking water. In principle, the treatment process is aimed at eliminating a wide variety of contaminants contained in the water as ions, organic materials, particles, microbes, and gas. The production of pharmaceutical water must meet the quality standards and ensure that the water to be used in accordance with the specifications. Water production is meant herein includes all processes such as storage and distribution systems. Table 1 below is a requirement that must be met by the pharmaceutical industry, especially in terms of the use of purified water.

Table 1. Purified Water Standard Requirements

Parameter	Purified Water (Eur. Pharm. + USP)	Highly Purified Water (Eur. Pharm.)	Water for Injection	
			(Eur. Pharm.)	USP
Conductivity at 25 °C	≤ 1,3 µS/cm	≤ 1,3 µS/cm	≤ 1,3 µS/cm	≤ 1,3 µS/cm
Heavy metal	-	0,1 ppm	0,1 ppm	-
Nitrate	-	0,2 ppm	0,1 ppm	-
Total Organic Carbon	< 500 ppb	< 500 ppb	< 500 ppb	< 500 ppb
Microbial limit	< 100 cfu/mL	< 10 cfu/mL	< 10 cfu/Mo	< 10 cfu/Mo
Endotoxines	-	< 0,25 Eu/mL	< 0,25 Eu/mL	< 0,25 Eu/Mo

Source: *United States Pharmacopeia [5]*

Generally, the water treatment process conventionally purified still using by the pharmaceutical industry in Indonesia [7]. Chemical process and refining the use of cation or anion exchange process in order to control the conductivity. Additionally, the chlorination process also is done to control the growth of bacteria. Therefore, this may potentially lead to instability of the quality of raw water that is produced, especially on several parameters such as pH, conductivity and total plate count (TPC). The instability of the resulting quality of raw water is assumed that the water treatment process does not always produce the raw water quality defect zero. So this may be an indication that the ability of the water treatment process was not optimal [4].

Various methods of approach have been developed in order to solve the problem of the instability of the water treatment process. One method that could potentially be used for quality control during the production is still in the process of the Six Sigma method. This method was first introduced by Motorola in about 1980 and is designed to reduce the occurrence of product defects [8]. Several studies using six sigma method have been applied in almost all fields of science, such as six sigma method can improve an organization's ability to carry out an environmental pollution reduction program in Portugal [9]. Furthermore, the use of six sigma method has also been applied in healthcare, where six sigma can reduce variability in clinical care and is able to improve the performance of the company [10]. In addition, the methodology of Six Sigma approach was used in reducing the incidence of occupational accidents in the collection of solid waste [11]. Six sigma consists of several basic values such as the principles of process improvement, statistical methods, customer satisfaction, continuous improvement and significant financial improvement. Reduction of the instability of the water treatment process as efforts to improve the environmental performance can be the target of continuous improvement. Thus, this study aims to apply Six Sigma methods in order to improve capabilities the water treatment process.

LITERATURE REVIEW

Six sigma is one method that combines the basics of lean manufacturing and six sigma philosophy into a single approach that is able to complete the problems in the production process [12]. Lean manufacturing and Six Sigma are two methods that have a structured procedure in the process of continuous improvement. Methods of Six Sigma is the latest approach to solving problems of quality and performance improvement. Several studies have proven that the Six Sigma method can achieve the maximum improvement in the company's performance, customer satisfaction, quality and reduce idle time and were able to reduce costs and increase the financial benefits [13]; [14]; [15]

Pande et al. provides a definition of Six Sigma as a mechanism for a comprehensive method and can be adjusted to the company in order to improve the achievement of corporate objectives [16]. Six Sigma method is a manifestation of the desire of the customers with quality improvements based on the data statistically processed in order to re-create the business process continuous improvement. The use of statistical tools and a few problem-solving techniques in the Six Sigma method is able to make the company gain a better standard. Meanwhile, the approach of lean methods plays a role in reducing unwanted activity and process variability on the organization [17]; [18].

Arnheiter and Maleyeff, underlines that the evolution of six sigma at any period of time will enable organizations to design and oversight on the improvement of business processes [19]. Defects and variation reduction and push towards a measurable advantage point view of six sigma. The expected target of continuous improvement is zero defects or defects per million opportunities (DPMO). Harry provide an understanding of the limits of 3.4 DPMO as defects deviations from the variability of the product or process [20]. Linderman et al. expressed that at each stage of the implementation of six sigma uses the specification of quality management and statistical analysis [21]. Sigma is a symbol of a standard deviation in statistical science dam shows a picture that measures the variability of the data is still distributed statistical mean values.

Six sigma method consists of five phases of DMAIC, such as Define-Measure-Analyze-Improve-Control [22]. DMAIC

methodology has been widely applied in manufacturing industries in order to obtain sustainable benefits in the future. Several activities are used, among other things, the identification, measurement, and reduction of sources of waste in the production process, optimizing the use of resources, improved performance, and increased production line. For instance, studies that apply DMAIC was done in manufacturing and fabrication industries in order to improve the quality and capable of decreasing the production cost [23]. Brief description and DMAIC phases as below:

- Define - the early stages where a problem is stated and defined in detail and clearly. This is an identification process carried out by the organization to get an overview of the problem in detail.
- Measure - This phase consists of the activities of data collection, measurement, and comparison of the actual problem.
- Analyze - phase of the process of identifying and characterizing the causes of defects and the sources of variation. Organizations- will determine the cause of process variation and the source of the problem and prioritize improvement opportunities in the future solutions.
- Improve - This stage is the implementation of improvements based on experiments for the reduction of defects and process variability. Organizations may implement the solution in order to improve the development of the implementation plan. At this stage, the organization may also define the process improvements will be performed.
- Control - the last stage of the DMAIC process that aims to provide assurance that the process has been strictly controlled in order to meet customer needs. The organization must be able to provide assurance that the process is monitored and implement continuous improvement.

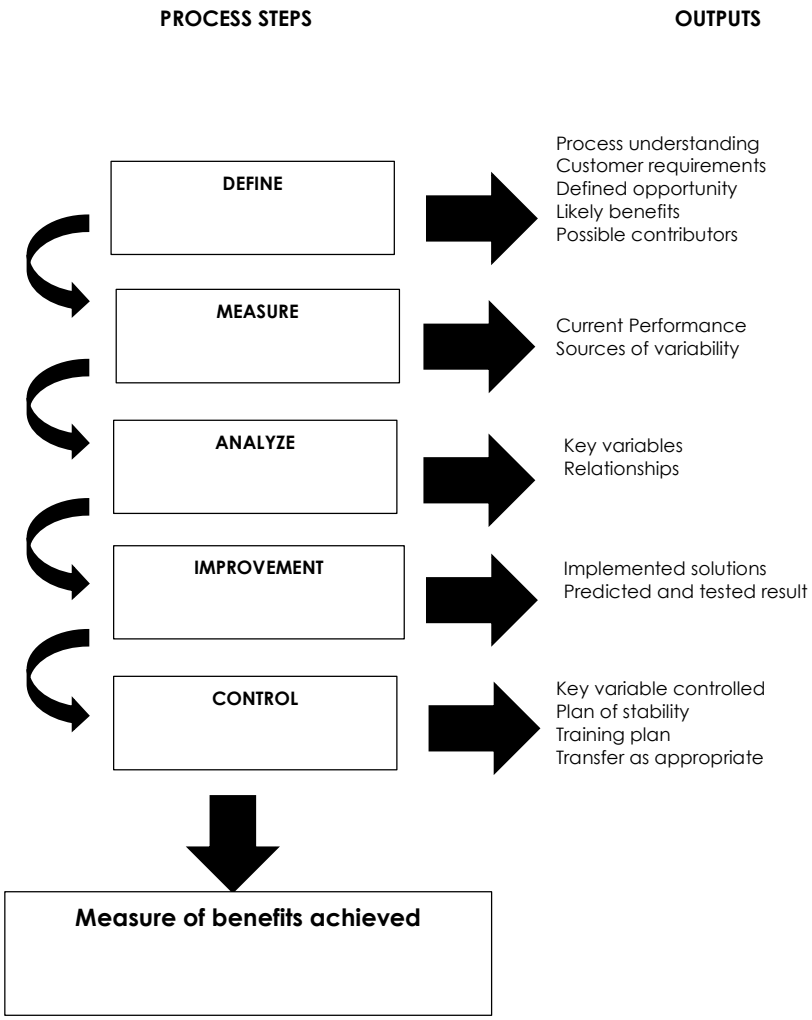

Figure-1. The Six Sigma DMAIC process and key outputs [22]

METHODOLOGY

The research was conducted to evaluate the water treatment process in the pharmaceutical industry. In addition, it also investigates the cause of cases of Out Of Specification (OOS) and proposes improvements through the implementation of six sigma method. The study begins by analyzing and identifying the factors that cause OOS in the processing of raw water. In order to provide the appropriate solution, problem-solving using six sigma methods that define, measure, analyze, improve and perform control. Firstly, is the stage of identification define stages, include: a preliminary study, the identification, and formulation of problems, determining research objectives, the study of literature and the determination method of completion. Secondly, the collection and processing of data, including Phase measure: data collection, the testing normality of the data, the preparation of individual control charts, process capability testing. Thirdly, analyze Phase with an analysis of the causes of deviations, and determine the cause of the dominant use Fishbone diagram and FMEA. Fourthly, improve Phase to determine the proposed improvements using tools 5W1H. Lastly, Phase control is the implementation of control activities after the improvement is done.

RESULT AND DISCUSSION

Define :

Define the first operational step in the process of Six Sigma quality improvement. This stage is the stage to define the process that will be discussed further before determining the quality characteristics and the needs of other customers. In the Define phase is to determine or define the goal of Six Sigma projects. The object of this study is the quality of the raw water used in the production process. The first phase consists a four-step process to consider, such as the investigation of the processes and work environment, SIPOC diagram, information gathering and problem statement. SIPOC diagram is used to determine the process illustrated in detail. SIPOC stands Suppliers, Inputs, Process, Outputs and Customers. SIPOC diagrams for quality control of raw water are shown in the table below.

Table 2. SIPOC diagram of quality control of raw water

Supplier	Input	Process	Output	Customer
Groundwater	Raw water	• Iron removal process • Chlorination • Purification	• *Aqua potable* • *Drinking water* • *Purified water* • *Water for injection.*	Household Canteen Laundry Laboratory Production department

As mentioned previously, the define stage is to explain the issues involved, the investigation and data collection. Based on observational data during the period October 2016 to December 2016 obtained the information that there are several sample parameters such as pH, conductivity and total plate count (TPC) is an unstable quality. Furthermore, observations during the past six months have also shown the presence of data beyond the limits established specifications (OOS). Thus, it can be assumed that the water treatment process is not always able to produce raw water quality defect zero, and this indicates the ability of the water treatment process is not optimal.

Measure :

The measure is the second stage of the DMAIC process. There are two procedures that can be done, for example, the concept of measuring the performance of the product and the concept of performance measurement process. Six Sigma approach is used in order to know in detail about the process of raw water treatment and the relationship of each cause.

a. Identification of Quality Characteristics

This stage is to identify the characteristics of quality which is essential for water quality control. In the table below are CTQ (Critical to Quality) of the production process water. Potential factors that cause deviation parameters of pH, conductivity and Total Plate Count (ALT) is the method of water treatment processes. This is due to the chlorination process steps that does not the controlled concentration of sodium hypochlorite is introduced into the basin. This also occurs in the process of reduction of the ions in the water (water purification) in the plant. The purification process of anion and cation mixed bed is not running optimally. This is probably caused by saturation ion-exchange resin in the system and a delayed regeneration of resin in the system the plant.

b. Performance Measurement Process

Normality test performed at each sampling site that is Room 114 (sample code R-114), and the chamber 139 (sample code R-139) with the amount of data each as much as 26 data taken from the data quality monitoring raw water weekly for 6 months from March 2016 to August 2016. The normality test used Kolmogorov-Smirnov. Based on the data sampling, then performed on the raw normality test water for each parameter measured as follows:

Table 3. Summary of normality using the Kolmogorov-Smirnov test

Parameter	***Sampling Point***	***p - Value***	**Interpretation**
ALT	Cream Processing (R-114)	*> 0,150*	Normal distribution
	Syrup Processig (R-139)	*> 0,150*	Normal distribution
pH	Cream Processing (R-114)	*> 0,150*	Normal distribution
	Syrup Processig (R-139)	*> 0,150*	Normal distribution
Conductivity	Cream Processing (R-114)	*> 0,150*	Normal distribution
	Syrup Processig (R-139)	*> 0,150*	Normal distribution

c. Measurement Process Capability

From the results of the normality test indicates that the data are normally distributed, then conducted an individual control chart average and moving range (I-MR) for each test parameter at each sampling point. I-MR control chart selected in the processing of this data because the data sample testing is individualized. The control chart is useful to ensure that the performance of the process is currently under control (in control), the operational process with good stability without the influence of specific causes.

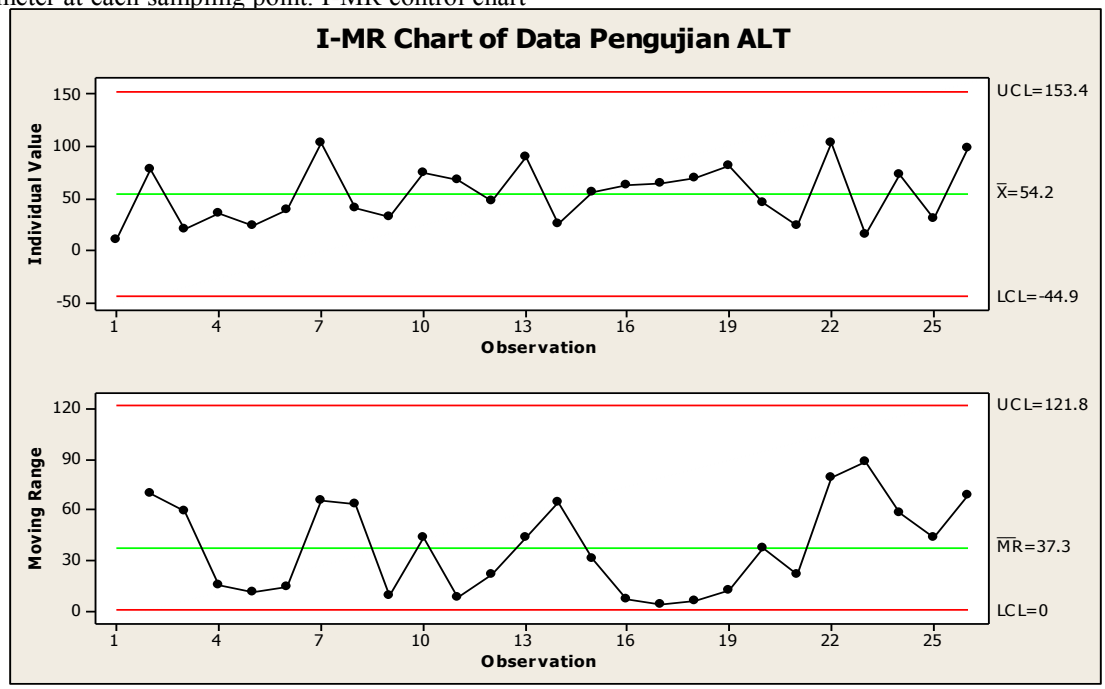

Figure 2. The IMR control chart for ALT (R-114)

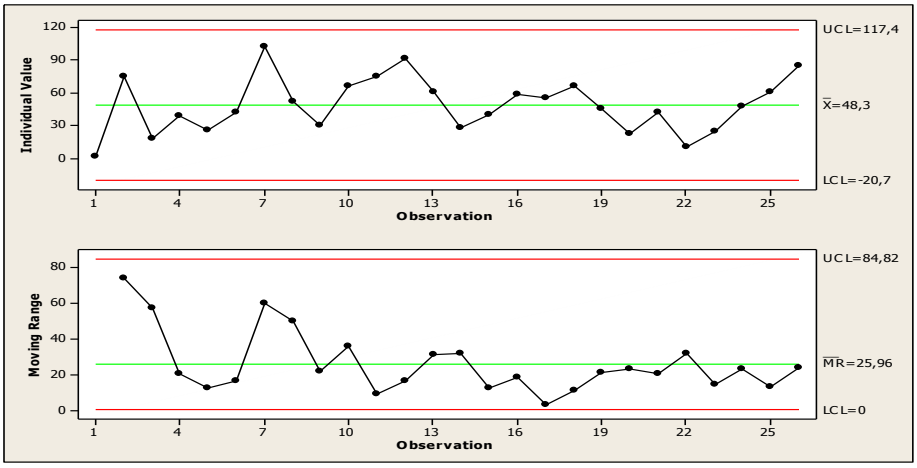

Figure 3. The IMR control chart for ALT (R-139)

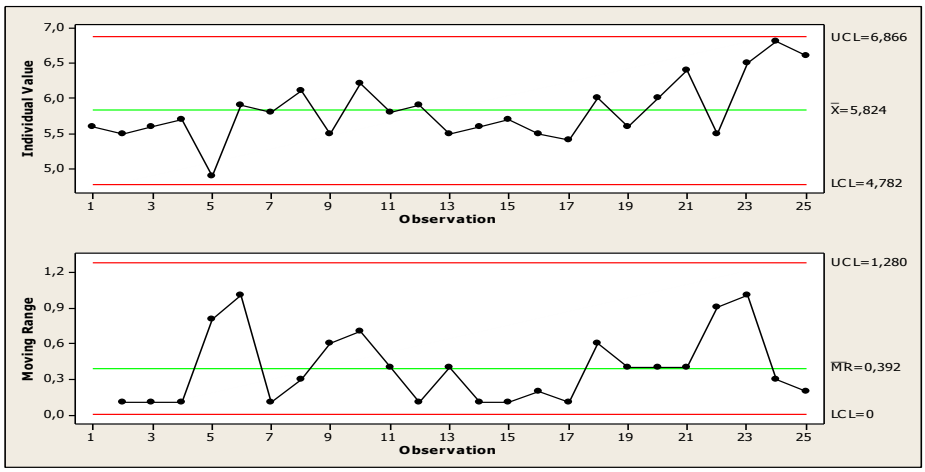

Figure 4. The IMR control chart for pH (R-114)

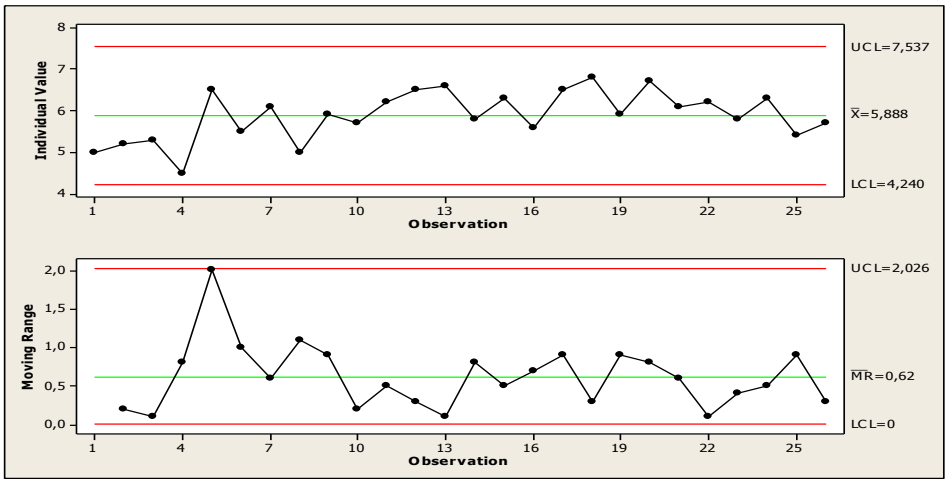

Figure 5. The IMR control chart for pH (R-139)

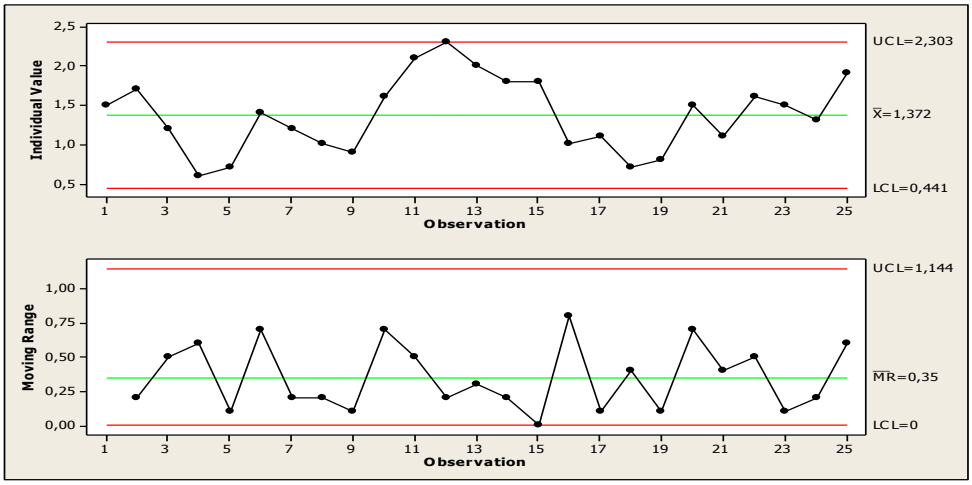

Figure 6. The IMR control chart for Conductivity (R-114)

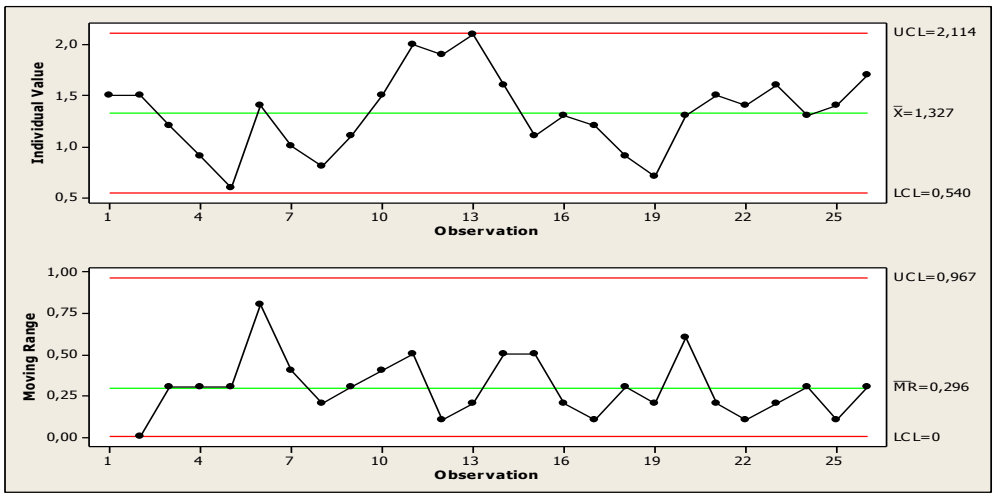

Figure 6. The IMR control chart for Conductivity (R-139)

The pictures above shows the general all parameters are within the control map. However, the conductivity parameters R-114 and R-139 there is a point which is outside the control chart limits. Thus, to facilitate analysis at a later stage, then the data is removed by assuming the presence of specific cause is then performed a recalculation.

Based on the results of the analysis using control chart IMR in all parameters, then analyzed capability the process. The results of the analysis are shown in the table below.

Table 4. Summary of Capability Process Analysis

Parameter	Capability Process *Index* Average	Failure Possible average of Products (ppm)
ALT	0,58	81.846,5
pH	0,67	41.873,7
Conductivity	-0,04	545.351,0
Average	0,40	223.023,7

Table 4 above provides information on the process capability analysis of raw water treatment. Furthermore, the table shows that the value of Cp and Cpk of all parameters smaller than 1. Thus, it can be concluded that the process indicated not having a good capability and did not meet the specification limits are expected with the possibility of producing out of specification approximately 223024 ppm.

Analyze :

The failure of raw water to meet the specifications defined by the total plate count, pH and conductivity can cause contaminated products produced or the irregularities. Thus, it is not safe to use and should be done reprocess. Further, pH is one factor to be considered given that the level of acidity of the water will greatly affect drug processing activities to be performed, such as, in conducting coagulation drugs, disinfection, and water softening. Another distraction of water with a low pH is believed to corrode water pipes that lead to

several chemical compounds turn into toxins that interfere with health. In addition, the effect of pH on the stability of the physical and chemical drug preparations with regard to the magnitude of the speed of the hydrolysis reaction catalyzed by hydrogen ions and hydroxyl ions is strongly influenced by pH. Further, hydrogen ions have a significant role in low pH, while hydroxyl ions have a role at high pH levels. In addition, the hydrolysis rate is significantly affected by hydrogen ion and hydroxyl ion on the pH of the medium. Thus, the condition of the water pH is too low or too high can drive the drug process becomes unstable. In addition, the high conductivity metal reflects the ionized water. The more ionized metal ions in water, it will encourage the higher of concentration the conductivity of the water. This can cause a chemical reaction or chemical bonding of the metal to the active substances or auxiliary substances. Thus, this condition is able to cause a decline in the stability of the drug.

Based on the explanation, it is necessary to find the root causes of the OOS. Thus, it can be done corrective actions and preventive failure of the water treatment process. To be able to find the root of the problem, brainstorming process is carried out at several stakeholders that have the capability to solve the problems of the raw water treatment process. As a result, the cause of the problem is shown in the figure a Fishbone diagram below.

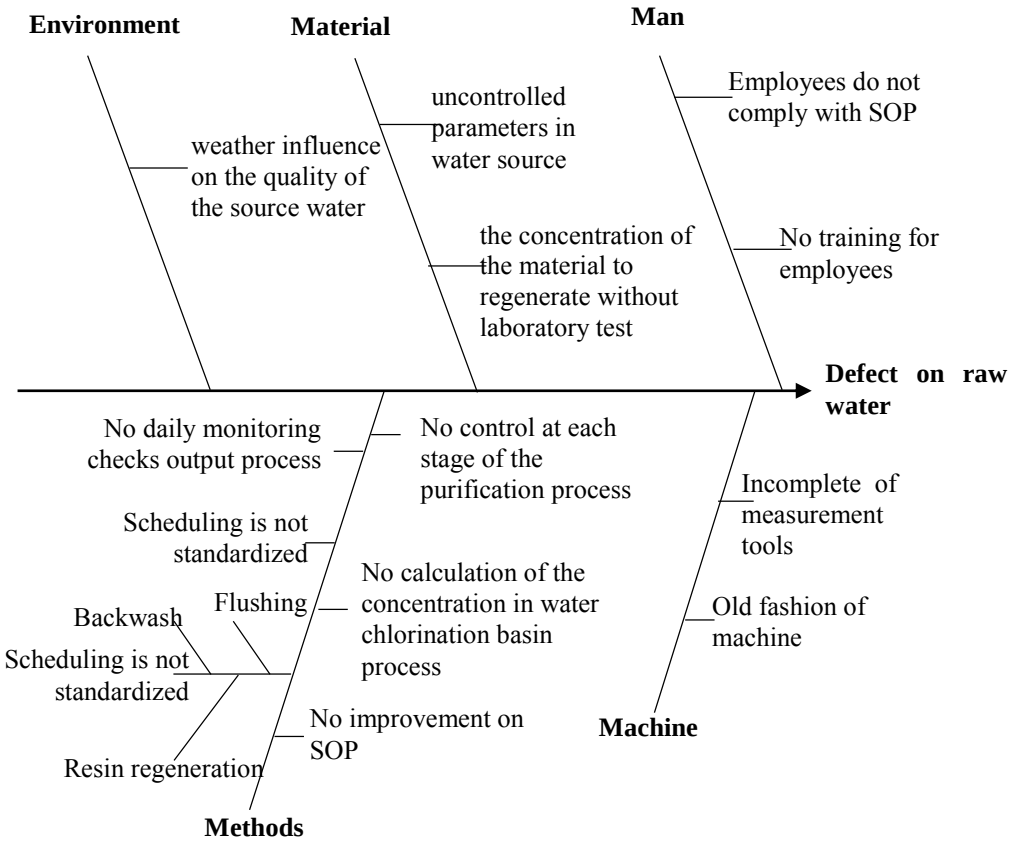

Figure 7. Fishbone diagram

Based on the results of brainstorming on a Fishbone diagram mentioned above, then the next is to determine the root cause of the problems potentially dominant cause irregularities quality and process. The method used to analyze at this stage is a Failure Mode Effect Analysis (FMEA). Failure mode and effects analysis (FMEA) were applied by NASA and subsequently applied to the automotive industry. This method can analyze potential defects of a product before it is consumed by the public.

Stamatis highlights that FMEA method has been applied to several types of industries such as automotive, aerospace and electronics [26]. Furthermore, the author also describes that this method consists of several stages such as identification, prioritization, elimination of potential failures or problems and faults of a system. To determine the dominant cause of the defect in the raw water, in this study used the technique FMEA and RPN values obtained in the table 5 below.

Table 5. Risk Priority Number (RPN) of water treatment process

Potential Failure Modes	***Risk Priority Number* (RPN)**
The failure smoothing reduction of ions positively and negatively charged in a tube mix bed	324
Failure of the reduction process positively charged ions and negatively in the cations and anions tube	288
Chlorine concentration in the basin is too low	252
Water output fail from the beginning process	162
Output water is not sterile	70
Pipe give contamination to water quality	70
Chloride ions present in Cations	64
Carbon filters are not able to absorb excess chlorine compounds from the water input	50
Samples contaminated on delivery	27
High microbial content of groundwater	24
A Sand filter is saturated	24
Water that will be tested contaminated by the environment	24
The concentration of chlorine compounds in gasoline is too high	18
High mineral content of the groundwater and fluctuating	16
Errors in laboratory test results	14

Based on an analysis using the Fishbone diagram and supported by the FMEA method can be concluded that there are several major problems that could potentially cause deviations raw water quality. For instance, the failure of the process of reduction of the ions in the system demi plant (cation-anion and mixed bed) and the ineffectiveness of the chlorination process in the basin. Further, this is because of two things, first, the regeneration of ion exchange resin in demi plant system is done without a good scheduling and measurable. Secondly, the process of chlorination of water in the basin that not calculated based on the concentration of the raw material and the target.

Improve :

In continuation of the DMAIC process, then at this step is the stage Improve processes to improve the quality of raw water. The 5W1H technique is used to establish the proposed improvements as presented in Tables 6 and 7 below:

Table 6. Summary of the results of the use of 5W 1H method in chlorination process

5W1H	**Type**	**Description**
What ?	The main purpose	Chlorination process that considers the expected concentration
Why ?	Reason uses	In order, the chlorination process is able to more effectively suppress the growth of microorganisms
Where ?	Location	Basin area
When ?	Sequences	November 2016
Who ?	People	Engineering and maintenance team
How ?	Method	Changes in methods of chlorination which was originally performed manually without concentration calculation. Then, using the chlorination process automation and the use of dosing pump by considering the target concentration. Therefore, it is necessary laboratory testing on the active substance content of each raw material in each process.

Table 7. Summary of the results of the use of 5W 1H method in chlorination process

5W1H	Type	Description
What ?	Main purpose	Changing the timing of the regeneration of ion exchangers
Why ?	Reason uses	The regeneration process is done with time and the right conditions, in order to saturate ion exchange resins can be avoided
Where ?	Location	*Demint plant area* (at the anions cations and mix-bed*)*
When ?	Sequences	November 2016
Who ?	People	Engineering and maintenance team
How ?	Method	Scheduling is made to control the process of regeneration of anion and cation resin in the mixed bed. Scheduling is based on the volume of water supply into the water system or the output of the cation-anion when awarding conductivity value above 10 us/cm

Control :

Based on the recommendations of the study, then made improvements to the water treatment system. Furthermore, the control of the process to ensure that improvement process in accordance with the recommendation. The control process is performed repeated analysis of the statistical control and capability index. As a result, as the table below:

Table 8. Summary of control chart after improvements

Parameter	Sample Code	Control Charts	Interpretation	Control limit	
				Description	value
ALT	R-114	I	*in control*	UCL	70,56
				GS	37,13
				LCL	3,69
		MR	*in control*	UCL	41,07
				GS	12,57
				LCL	0
	R-139	I	*in control*	UCL	70,83
				GS	35,88
				LCL	0,92
		MR	*in control*	UCL	42,94
				GS	13,14
				LCL	0
pH	R-114	I	*in control*	UCL	6,358
				GS	5,712
				LCL	5,067
		MR	*in control*	UCL	0,7935
				GS	0,2429
				LCL	0
	R-139	I	*in control*	UCL	6,509
				GS	5,787
				LCL	5,066

		MR	*in control*	UCL	0,8868
				GS	0,2714
				LCL	0
Conductivity	R-114	I	*in control*	UCL	1,2919
				GS	0,95
				LCL	0,6081
		MR	*in control*	UCL	0,4201
				GS	0,1286
				LCL	0
	R-139	I	*in control*	UCL	1,2794
				GS	0,9375
				LCL	0,5956
		MR	*in control*	UCL	0,4201
				GS	0,1286
				LCL	0

The results of the analysis of the control chart, then become a guide to the process capability analysis. Thus, the result of the capability process after the improvement is shown in Table 8 below:

Table 9. Cpk Index after improvements

Parameter	Capability process *Index* Average	The possibility of defects average of raw water (ppm)
ALT	1,07	735,5
pH	1,10	500,2
Conductivity	1,04	901,7
Average	1,07	712,5

From the summary of the results of the capability process analysis after improvement as illustrated in Table 8 above, the water treatment process demonstrated significant changes in capability. The average index of the whole process capabilities testing parameters increases and the probability that OOS of raw water decreased. The data capability process index and of raw water OOS presented in Table 10 below:

Table 10. Comparison of Capability process values before and after Improvement

Parameter	Average of Capability process *Index*		Probability of raw water that OOS (ppm)	
	Before	After	Before	After
ALT	0,58	1,07	81.846	735,5
pH	0,67	1,10	41.873	500,2
Conductivity	-0,04	1,04	545.351	901,7
Average	0,40	1,04	223.023	712,5
Sigma Level	-	-	2,26	4,69

Table 10 above illustrates the change process capability index average improvement of around 0.40 before rising to an average of 1.07 after repair. This can be interpreted in an increase in the capability of the water treatment plant and the

possibility of the system to produce out of spec occur initially declined approximately 223,023.7 ppm to about 712.5 ppm. In addition, the increase in the value of sigma that initially rose roughly 2.26 to 4.69.

CONCLUSION

Water treatment process in several test parameters such as pH and conductivity are not in statistical control. This indicates instability of the water treatment process. Process capability analysis results indicate that the water treatment plant does not have a viable process capability index Capability process value approximately 0.40 and the possibility of generating of raw water systems that OOS approximately 223 023 ppm. The deviation caused by the failure of the process of reduction of the ions in the system demi plant and the ineffectiveness of the chlorination process basin. There are two factors as the main cause of such failures, the first is the regeneration of ion exchange resin that done without a good scheduling and measurable, the second is the method of chlorination of the water in the basin did not calculate based on the concentration of the raw material and the target. Recommendations for improvement is to implement the regeneration of ion exchange resins explanation on demi plant system that considers the volume of water entering. Furthermore, the method of chlorination of the water basin should also be based on the calculation of the concentration of Sodium hypochlorite. This study is a starting point for process control in the pharmaceutical industry of raw water using six sigma applications, it is necessary to further research on the relationship between the dominant factors of the defect of raw water.

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