Reducing of Defects in the Drug Tablets Production Process with DMAIC to Improve Quality – Study Case of Pharmaceutical Industry

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Abstract. The high defect and unstable of defects the company in 2017 amounted to 0.27% while the amount allowed by this company was 0.10%. In This research was carried out in a Pharmaceutical Industry with the purpose of reducing the product spots drug tablets, the research method uses the DMAIC stages Define, Measure, Analyze, Improve and Control. The tools used are SIPOC diagrams, pareto diagrams, P charts, minitabs to calculate sigma levels and improvement with FMEA. The number of reject spots for tablets in 2018 was 0.28% and the sigma level was 4.63, then after analysis and DMAIC the reject rate was reduced to 0.0081% and sigma level 5.45.

1. Introduction
The pharmaceutical industry in 2002 pulled profits that far exceed other industries and accounted for profits five-and-a-half times greater than the median for all industries [1]. Drug discovery and development it’s however very expensive and the industry is plagued with drug failure during the development stage, including the cost of failures, developing and taking a new drug to market [2].
The competition of the pharmaceutical industry is increasingly higher the need for the pharmaceutical business to be able to always use a competitive strategy that is healthy and relevant to the development of the environment in order to be able to maintain the product brand against related companies and improve quality so that the resulting production increases [3]. Six Sigma's core goals for improving operating performance, through operations [4]. Six Sigma increases customer needs, increases data payments, and improves the process of producing, reducing or reducing defects, reducing irregularities in the process, and increasing capacity [5].
Quality control is an activity that is controlled and implemented by monitoring outputs, comparing with standards, interpreting differences and taking action to readjust those processes so that they are in accordance with the standards [6]. The purpose of study is to analyze the factors that cause differences in drugs and find the right solution to overcome this problem.

2. Method and materials
Quality is an activity that is controlled and implemented by monitoring outputs, comparing with standards [6]. Quality is the totality of features and characteristic of a product or service that bears on it’s ability to satisfy started or implied need [7]. Six Sigma is a new management tool used to replace Total Quality Management, very focused on quality control. Six sigma are also called comprehensive systems - that is, strategies, disciplines, and tools - to achieve and support business success. Six Sigma is called a strategy because it focuses on increasing customer satisfaction, called disciplines because it follows the formal model, namely DMAIC and tools because it is used in conjunction with others, such as Pareto Charts and Histograms [8]. Define is the phase of determining the problem. Measure is the phase of measuring the current level of
performance. The analysis phase is the phase of finding and determining the root or cause of a problem. The problems that arise are sometimes so complex that it confuses what we will and won’t solve. Development (improve) is the phase of improving process and eliminating the causes of defects. Control is the phase of controlling the performance of the process and ensure defects do not reappear.

The high reject in 2017 became a major problem in this company, then researchers conducted discussions with several departments to find solutions to problems using reject 2017 and identification in 2018 then the application of the solution in 2019. Six Sigma might be able to help the pharmaceutical industry moderate and improve the quality management system and overall performance in continuous improvement and operational excellence should be part of the overall effort to improve the quality of medicinal products [9]. The Six Sigma approach has a positive impact on the Lead-Time Department of health, where customer satisfaction can be met in line with company targets, one of which is improving service quality [10]. In accordance with the discussion discussed above, improvement in quality is not only seen in the final result but also in the process. Then there is another research that has a positive impact [11], the results of improvement with 5W+1H can reduce of reject biscuits by using the DMAIC method. Six Sigma is proven to provide solutions for manufactur as has been done by some previous researchers, A causal diagram, Ichigawa, Fishbone and FMEA can reduce product defects [12]. Reducing the nonconforming products research by using the Six Sigma method: A case study of a polyester short cut fiber manufacturing in Indonesia The process increased from 2.2 sigma to 3.1 sigma [13]. Innovation and technology improvement of hydrant pillar welding process to decrease the defect ratio approach to DMAIC method and quality increases [14]. The results of eliminating cost of poor quality of 6.2 Lakhs and percentage rejection decreased from 6% to 2% [15]. The FMEA tool is one of the most widely used tools for the industry to analyze the root cause of the system and increased printing machine productivity using OEE and FMEA [16, 17].

3. Results and discussion

The production process at this company is generally divided into several preparations such as injection drugs, liquid, drug tablets and etc. The process generally starts from the new product development, purchasing, warehouse, QC, PPIC, production, packaging, QA. This research only focuses on the production tablet. The research data 2017 which are as follows:

| No  | Month    | Production     | Defect | %    |
|-----|----------|----------------|--------|------|
| 1   | January  | 12.768.700     | 30.340 | 0.27%|
| 2   | February | 7.090.960      | 21.289 |      |
| 3   | March    | 12.162.820     | 32.989 |      |
| 4   | April    | 12.300.645     | 32.726 |      |
| 5   | May      | 11.265.099     | 32.183 |      |
| 6   | June     | 9.967.893      | 19.099 |      |
| 7   | July     | 12.698.720     | 31.200 |      |
| 8   | August   | 10.088.987     | 31.121 |      |
| 9   | September| 12.455.611     | 32.234 |      |
| 10  | October  | 11.124.509     | 33.590 |      |
| 11  | November | 12.768.234     | 32.490 |      |
| 12  | December | 7.785.430      | 31.090 |      |
| Total|         | 132.477.608    | 360.351| 0.27%|

Table 2. Internal Defect data 3 Periode in 2018

| No  | Month    | Production     | Defect | Percentage |
|-----|----------|----------------|--------|------------|
| 1   | October  | 12.824.509     | 30.340 | 0.24%      |
| 2   | November | 11.959.588     | 33.490 | 0.28%      |
| 3   | December | 9.204.509      | 32.090 | 0.35%      |
| Total|         | 33.988.606     | 95.920 | 0.28%      |
From the table 1 shows that the percentage of defects in the production process of drug tablets is still high at 0.27%, while the defect tolerance allowed is below 0.10% of total production. The percentage of defects is the special task of all parties to find out the existing problems and find solutions so that the problem can be solved. So the researchers taking data at table 2 is three months at the end of 2018 by applying DMAIC in pharmaceutical industry.

3.1. Define
At the stage of defining the activities carried out to identify problems using SIPOC and CTQ. The following sipoc and CTQ diagrams in this study:

Weighing is the process of weighing raw materials. Mixing is the process of mixing active substances, additives and others according to the formulation. Granulisation is the process of grinding or refinement as homogeneous. Materials that have been through the granulisation process are sampled by IPC for the analysis process. The analysis process includes, water content, dissolution and content of active substances. Core is the process of granulisation which was originally in the form of powder and then formed into tablets, such as round, oval and other shapes. Results were sampled again by IPC for analysts, which included tablet hardness testing, tablet disintegration test time, tablet thickness, were they still consistent or did a change occur that caused the drug level to not meet the standards. Coating is a drug lubrication process with the purpose of protecting, for example protecting from stomach acid, increasing stability when stored, covering up bad taste and others. The CTQ determination uses the Pareto diagram as shown in Figure 2. From the Pareto diagram it was found that the highest defects were spot drug tablets, Motling Tablets, Collapsed and Peeled, so due to limited research time the four defects were damaged again by focusing on the problem namely Spot Medication Tablets.

3.2 Measure
In this stage, mapping of defects in the production process using the p chart and sigma level measurement is used to determine the ability of the process before improvement.
Table 3. Sigma Level data 3 Periode in 2018

| Month | Production | Spots Drug | DPU   | DPO   | DPMO  | YRT         | YNA        | ZLt      | Zst      |
|-------|------------|------------|-------|-------|-------|-------------|------------|----------|----------|
| Oct   | 5.205.673  | 9.522      | 0.001829 | 0.000915 | 914,580000 | 0.998173   | 0.999086 | 3,116841 | 4.62     |
| Nov   | 10.464     | 4.744.888  | 0.002205 | 0.001103 | 1102,660000 | 0.997797   | 0.998898 | 3,061270 | 4.62     |
| Dec   | 7.089.410  | 12.283     | 0.001733 | 0.000866 | 866,290000  | 0.998269   | 0.999134 | 3,132711 | 4.64     |
| Total | 12.305.547 | 4.766.693  | 0.387361 | 0.193681 | 193680,662875 | 1,473092   | 0.999039 | 3,102130 | 4.63     |

3.3 Analyze
The analyze phase is the third stage of the DMAIC cycle in the six sigma method, which is an analysis of the measurement results of the measure stage, in this stage an couse and effect diagram and NGT (nominal group technique) activity is carried out.

3.4 Improve
The improve phase is the fourth stage in the six sigma method, which is the stage of corrective action for the causes of the problem (root problem) that have been obtained in the analyze phase. In this study the stages of improving using the FMEA (failure mode effect analysis) tool. Namely by looking at the RPN value sequentially from highest to lowest which will be the order of its improvement.
Table 5. Value RPN with FMEA

| Type          | Potential Failures | Potential Causes of Failure                                                                 | S  | O  | D  | RPN | Solution                                      |
|---------------|--------------------|---------------------------------------------------------------------------------------------|----|----|----|-----|-----------------------------------------------|
| Methode       | Spots Drug Tablets | The making of a coating solution is not explained in detail                                  | 3  | 3  | 3  | 27  | Revised BPO PO with the addition of making in detail |
|               | Assay is Low       | The formula hasn’t been stabilized yet                                                      | 3  | 1  | 1  | 3   | Validasi formula                             |
|               | Chipped Tablets    | Inlet and outlet temperatures are not noticed                                               | 3  | 3  | 2  | 18  | Changes in inlet temperature (80-85) and outlet temperature (60-65) |
|               | Thickness not      | Changes to the specifications of the tablet core have not been revised                      | 1  | 3  | 1  | 3   | Monitoring of change control Specifications |
|               | Standard           | Nozzle distance from the core is too close (17-20)                                          | 1  | 3  | 1  | 3   | Change the nozzle distance 25cm              |
| Machine       | Binding            | RH Machines are not required                                                                | 3  | 3  | 1  | 9   | The addition of RH became 32 C in BPO PO     |
|               | Sticking           | When the process does not pay attention to LOD and RH                                      | 1  | 1  | 3  | 3   | LOD checking process is carried out before the core process |
| Material      | Motting            | Material is hygroscopic                                                                    | 3  | 3  | 2  | 27  | Substitution of material                    |
|               | Crumbling          | Protection for better product sterility                                                     | 3  | 3  | 2  | 27  | Data trand to determine the weight per tablet coating results |
| Environment   | Colour             | Queued core machines at low RH facilities                                                   | 3  | 2  | 2  | 12  | Hygroscopic granules are processed first     |

The FMEA table contains 10 problems that are recommended to be fixed according to the schedule provided by the company, but not all problems can be solved. Then the RPN calculation is used as follows:

\[
\text{Critical RPN} = \frac{\sum \text{RPN}}{\sum \text{Risk}} = \frac{132}{10} = 13.2
\]

From the critical RPN calculation, there are 4 RPN values that have a value above 13.2 and then improvements are made according to the solution in the table.

3.5 Control

The control phase is the last stage in the six sigma method where in the control phase is carried out the process control activities after improvement. p chart, and performance baseline (sigma level) again to find out the success rate of improvement implementation. In this research, the control stage is carried out by taking production data and defective products in March, April and May 2019. With the same calculation as in the measure stage, a p chart and sigma level:

![P Chart of Defect](image)

Figure 5. P Chart of Spots Drug Tablets March - May 2019

From the picture above the results of the p chart shows that the results of the production process are controlled.
Table 6. Sigma Level March 2019

| Month | Production | Defect | CTQ | DPU     | DPO     | DPMO   | YRT     | YNA     | ZLt     | Sigma |
|-------|------------|--------|-----|---------|---------|--------|---------|---------|---------|-------|
| March | 8.102.594  | 835    | 2   | 0.000103| 0.000052| 51,526709| 0.999897| 0.999948| 3.883293| 5.38  |
| April | 8.968.047  | 779    | 2   | 0.000087| 0.000043| 43,431976| 0.999913| 0.999957| 3.924631| 5.42  |
| May   | 9.379.401  | 499    | 2   | 0.000053| 0.000027| 26,600846| 0.999947| 0.999973| 4.041099| 5.54  |
| Total | 26.450.042 | 2.113  | 2   | 0.000081| 0.000041| 40,519843| 0.999919| 0.999959| 3.949674| 5.45  |

4. Conclusion

From the above research it is concluded that the reduction of defective products with the DMAIC method can positively affect the quality of the drug. The reject rate in 2017 was 0.27% then the reject rate at the end of 2018 was 0.28 with a sigma level of 4.63 and then the DMAIC method was applied and the reject rate dropped to 0.0081% and the sigma level to 5.45.

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