

Improving Vaccine Product Quality Using the Six Sigma DMAIC Method: A Case Study at PT Vaksindo Animal Nusantara

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ABSTRAK

Vaccindo merupakan produsen vaksin lokal pertama dan terpercaya untuk memenuhi kebutuhan vaksin para petani di Indonesia. Penelitian ini untuk mengetahui kualitas vaksin IBH yang masih dalam tahap uji coba produksi di PT. Vaksindo dan untuk mengetahui penerapan pengendalian cacat dengan metode Six Sigma pada produk vaksin cacat. didapatkan konsentrasi virus yang dihasilkan rata-rata tidak masuk ambang batas minimal standar yang ditetapkan yaitu 7,0 TCID₅₀/0,1 mL pada tahap uji coba, Defect Per Million Opportunity (DPMO) sebesar 826408,73 yang artinya dalam setiap juta kali produk yang dihasilkan pada setiap produksi memiliki produk cacat sebesar 826408,73, jika dikonversikan ke dalam tabel sigma nilai DPMO bahkan tidak masuk pada level sigma pertama yaitu sebesar 690.000 DPMO yang artinya proses yang dilakukan dalam proses produksi vaksin IBH oleh PT. Cakupan Vaksindo masih dibawah 30,9% untuk memperbaiki hal tersebut, perbaikan yang dilakukan seperti pengujian kadar virus titrasi VCT pada setiap sampel pasca panen dan pra produksi untuk menjaga kualitas antigen yang dihasilkan, serta perbanyak benih dilakukan pada batas maksimal yang dapat diperoleh agar pada saat diperbanyak dengan antigen, nilai titer atau konsentrasi virus tidak turun dan tetap standar.

Kata kunci: penerapan pengendalian cacat dengan metode six sigma pada produk vaksin yang tidak lolos uji

ABSTRACT

Vaccindo is the first and most trusted local vaccine producer to meet the vaccine needs of farmers in Indonesia. This study was to determine the quality of IBH who is still in the trial phase, vaccine production at PT. Vaksindo and to determine the application of defect control with Six Sigma method on defective vaccine products. to obtain the concentration of the virus produced on average does not enter the minimum threshold of the standard set, that is 7.0 TCID₅₀ /0.1 mL in trial phase, Defect Per Million Opportunity (DPMO) is 826408.73, which means that in every million times of product produced in each production has a defective product of 826408.73, if it is converted into a sigma table the DPMO value does not even enter the first sigma level is the value of 690,000 DPMO, which means the process carried out in the IBH vaccine production process by PT. Vaksindo coverage is still below 30.9% to improve this, improvements are such as testing the level of viruses of VCT titration in each sample post harvest and pre production to maintain the quality of the antigen produced, as well as propagation seed is done at the maximum limit that can be obtained so that when propagated to antigen, the titer value or concentration of the virus does not go down and remaining standard.

Keywords : application of defect control with the six sigma method on vaccine products that did not pass the test

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INTRODUCTION

The advancement of technology and the evolution of consumer behavior have significantly influenced how customers choose products. In addition to competitive pricing, quality has become a critical determinant in consumer decision-making. Achieving high product quality, particularly with a target of near-zero defects, often requires considerable financial investment (Psarommatis, Sousa,

Mendonça, & Kiritsis, 2022). Therefore, consistent improvement of product and process quality throughout the production system is essential for companies aiming to maintain competitiveness and ensure customer satisfaction. Through effective quality control, companies can improve their ability to prevent product defects, reduce material and labor waste, and enhance overall productivity (Lindström et al., 2019; Sukarma, Hendra, Effendi, & Mohamad, 2020).

PT. Vaksindo Satwa Nusantara is a research-oriented company engaged in the production of high-quality animal vaccines. Established in 1982 as Indonesia's first private animal vaccine manufacturer, the company began production in 1983 following the overseas training of Indonesian veterinarians in Japan. This training focused on advanced techniques in vaccine production, quality control systems, and the management of Specific Pathogen Free (SPF) farms. By 2018, Vaksindo had grown substantially, employing more than 30 veterinarians and extending its market reach beyond Indonesia. The company made its first international export to Pakistan in 1995, followed by expansion into countries such as Thailand, the Philippines, Sri Lanka, Malaysia, Nepal, Syria, Myanmar, and Nigeria (Company Profile, 2019).

Despite the implementation of quality assurance systems managed by the Quality Control (QC) and Research & Development (R&D) divisions, the company continues to face issues with product defects. Several complaints have been received from customers concerning substandard vaccine batches, particularly involving the Inclusion Body Hepatitis (IBH) vaccine. As indicated by internal data for the period January to June 2019, fluctuations in antigen production results suggest that the quality levels have not consistently met the required standards (PT. Vaksindo, 2019). This situation necessitates a deeper investigation into the underlying causes of vaccine defects.

This final project research is conducted within the R&D division and applies the Six Sigma methodology to the IBH vaccine production process. Six Sigma is a data-driven approach for eliminating defects and improving process capability (Pyzdek & Keller, 2014). The IBH vaccine targets a viral disease that affects the liver of poultry, especially broiler chickens. The disease is caused by Adenovirus type 11, which leads to liver cell damage and the formation of inclusion bodies (OIE, 2021). Given the recurring quality issues, a structured problem-solving framework is essential to identify and control the sources of variation in the manufacturing process.

The research addresses the following questions: (1) What are the key factors contributing to the failure of vaccine quality tests during production? and (2) How can the quality level of vaccine production be evaluated and improved using the DMAIC (Define, Measure, Analyze, Improve, Control) cycle within the Six Sigma framework? The objectives of the study are, first, to assess the current quality performance of the IBH vaccine production at PT. Vaksindo, and second, to explore how the application of Six Sigma tools can assist in minimizing defects and enhancing product reliability.

In the pharmaceutical and biotechnological industries, especially in the field of veterinary vaccine production, maintaining and improving product quality is critical to ensuring safety, efficacy, and customer satisfaction. As global competition intensifies, manufacturers are under increasing pressure to produce high-quality products while minimizing costs and operational inefficiencies. This context underlines the importance of robust quality management systems such as Six Sigma, which offers structured, data-driven approaches to identify, analyze, and eliminate defects in production processes (Clancy, O'Sullivan, & Bruton, 2023).

1. Quality in Pharmaceutical Manufacturing

Quality in pharmaceutical and vaccine manufacturing is not merely a marketing aspect; it is a regulatory and ethical necessity. According to the World Health Organization (WHO), vaccines must meet strict standards of quality, safety, and efficacy before being approved for use (WHO, 2020). The adoption of Good Manufacturing Practices (GMP) and continuous quality monitoring are essential to ensure compliance with both national and international standards (FDA, 2011). In this regard, variability in production, such as those related to antigen concentration or contamination, must be tightly controlled (Kumar & (Huang, Irfan, Fatima, & Shahid, 2023).

2. The Role of Quality Control and Assurance

Quality control (QC) focuses on identifying defects after a product is developed, whereas quality assurance (QA) is preventive and aims to improve the process to avoid defects (Kirwan et al., 2022). Both are integral to ensuring the consistent quality of vaccine production. For example, inactivated vaccines like IBH are susceptible to quality failures due to fluctuations in virus concentration, pH levels, and sterility parameters (Morrow & Fehler, 2004). Hence, quality management systems must be integrated into the entire production lifecycle (Kirwan et al., 2022).

3. Six Sigma as a Quality Improvement Tool

Six Sigma, first popularized by Motorola and later championed by General Electric, is a systematic methodology aimed at improving process performance and reducing variability (Coughlin & Posencheg, 2023). It operates on a five-phase framework known as DMAIC—Define, Measure, Analyze, Improve, and Control. The method is especially useful in highly regulated environments where defect reduction and process stability are paramount (Antony, 2006). In pharmaceutical manufacturing, Six Sigma has been applied to reduce batch rejection rates, improve equipment reliability, and optimize resource usage (Coughlin & Posencheg, 2023).

4. Applications of Six Sigma in the Pharmaceutical Industry

Numerous studies demonstrate the effectiveness of Six Sigma in pharmaceutical production. For instance, (Haekal, 2023) reported a 40% reduction in defects in a vaccine manufacturing plant after Six Sigma implementation. Similarly, da Silva, de Oliveira, and Magalhães (2025) applied Six Sigma to minimize variation in tablet weight in a pharmaceutical unit, resulting in improved compliance and

reduced wastage. These examples underscore the versatility of Six Sigma in different pharmaceutical settings, including vaccine production.

5. Factors Causing Vaccine Defects

Several critical factors contribute to defects in vaccine production. These include improper sterilization, inadequate antigen concentration, contamination, and errors in the filling and packaging stages (Haque & Islam, 2021). Human error and variability in raw materials are also significant contributors (Gogtay et al., 2013). Identifying the root causes of these defects through analytical tools such as fishbone diagrams, Pareto charts, and statistical process control (SPC) can help prioritize improvement initiatives (Bellavite, 2020; Yu, Taraban, & Briggs, 2021).

6. Process Stability and Statistical Quality Control

Process stability is a foundational requirement for quality assurance in vaccine manufacturing. Tools such as control charts help monitor process performance over time and detect variations that could lead to defects (Montgomery, 2020). Statistical quality control (SQC) techniques can be integrated into the Six Sigma framework to provide real-time feedback and enhance process robustness (Juran & Godfrey, 1999). For example, p-charts and c-charts are particularly useful in identifying defect trends in batch processes (Kwilinski & Kardas, 2023).

7. Root Cause Analysis in Quality Failures

Root cause analysis (RCA) is essential in the Analyze phase of Six Sigma. It helps identify fundamental issues in the production process that lead to quality failures. Techniques such as 5 Whys, Fault Tree Analysis (FTA), and Failure Mode and Effects Analysis (FMEA) are widely used to dissect and understand process failures (Barsalou, 2023; Lima et al., 2021). In the case of vaccine production at PT. Vaksindo, these tools can aid in discovering specific issues such as non-sterile environments or inconsistent mixing procedures that affect antigen quality.

8. Defect Prevention and Cost Reduction

Defect prevention is more cost-effective than defect detection. The cost of poor quality (COPQ) includes internal failure costs (scrap, rework), external failure costs (returns, complaints), appraisal costs (inspection), and prevention costs (training, process design) (Feigenbaum, 1991). Six Sigma aims to reduce COPQ by emphasizing defect prevention through root cause elimination and process improvement (George et al., 2005). For vaccine producers, this translates to higher productivity, fewer recalls, and stronger customer trust (Sadikin, 2023).

METHODS

This study employs a quantitative research approach using the Six Sigma methodology, specifically the DMAIC (Define, Measure, Analyze, Improve, Control) framework, to evaluate and improve the quality performance of the Inclusion Body Hepatitis (IBH) vaccine production process at PT. Vaksindo

Satwa Nusantara. The research is conducted within the company's Research and Development (R&D) division, focusing on analyzing internal quality data, particularly defect rates observed in the IBH vaccine batches produced during the January–June 2019 period. In the Define phase, the problem of vaccine defects is identified through customer complaint data and internal reports, which serve as the basis for formulating the project charter and identifying critical-to-quality (CTQ) characteristics. The Measure phase involves collecting data on antigen levels, production parameters, and the number of defective units to quantify the current sigma level and process capability. In the Analyze phase, tools such as the fishbone diagram, Pareto chart, and Failure Mode and Effect Analysis (FMEA) are applied to identify and prioritize the root causes contributing to vaccine defects. The Improve phase focuses on developing and implementing corrective actions, including process standardization, operator training, and machine calibration, to reduce variability and prevent reoccurrence of defects. Finally, in the Control phase, control charts and standard operating procedures (SOPs) are used to monitor the performance of the improved process and ensure its sustainability. Data analysis is supported by the use of Microsoft Excel and Minitab software to perform statistical analysis and visualize process improvements. The overall goal of this methodology is to enhance product quality, minimize defects, and improve production efficiency, thereby aligning with PT. Vaksindo's commitment to delivering high-quality veterinary vaccines.

RESEARCH RESULTS AND DISCUSSION

Discussion

This research is for applying *Six Sigma* in the manufacture of IBH vaccine carried out at PT Vaksindo Satwa Nusantara with the aim of obtaining good vaccine results, it is necessary to implement several methods in *Six Sigma*, one of which is the DMAIC Cycle,

(*Define, Measure, Analytic, Improve, Control*) This method will provide the author with the information needed for product development and maintaining product quality during mass production.

1. *Define* Phase

Before looking for possible causes of vaccine defects, we will first display the classification of defects that occur in vaccine products.

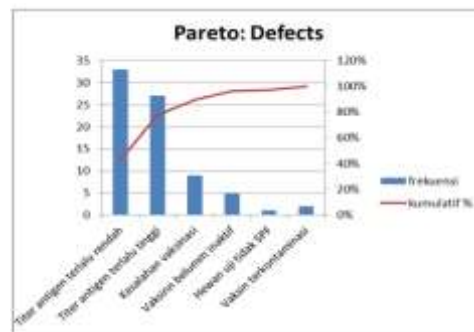
The classification of vaccines that have selling power or meet the specifications set by the company are as follows:

- a. A vaccine that has the ability to produce sufficient *antibodies to fight disease viruses in the body*.
- b. Vaccines must pass health tests on the animals that have been vaccinated.
- c. Vaccines must not cause side effects in animals or humans.
- d. The vaccine must pass the test from the supervisory body of the Republic of Indonesia government, in this case the relevant agency is BBPMSOH.

The classification of vaccines that have less marketability or do not meet specifications is as follows:

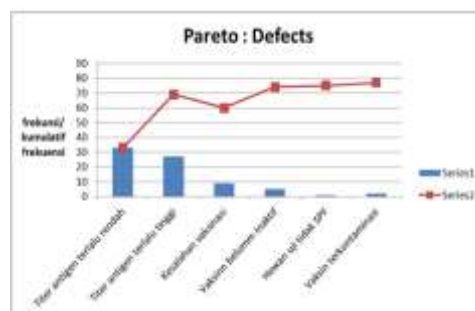
- Vaccines do not produce *antibodies* in animals to fight disease viruses.
- The vaccine did not pass either laboratory tests or cage tests.
- Causes side effects in animals and humans who have consumed animals, after the animals have been vaccinated.
- There is no certification from a certified government body such as BBPMSOH.

A Pareto diagram can be made to find out how big the influence of each factor is in causing the failure of the *Safety-Potency test* that was carried out. The following is the Pareto diagram:



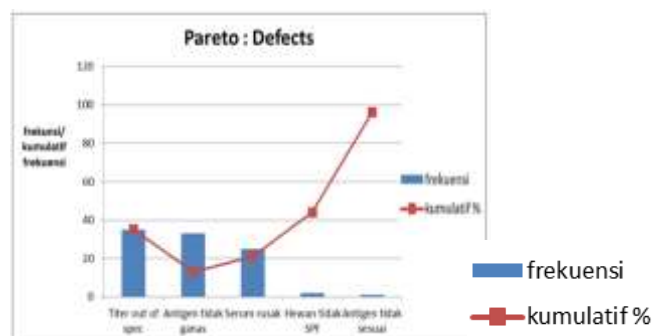
(Source: Own data processing)

Figure 4.14 Pareto diagram of *safety test* with cumulative frequency values



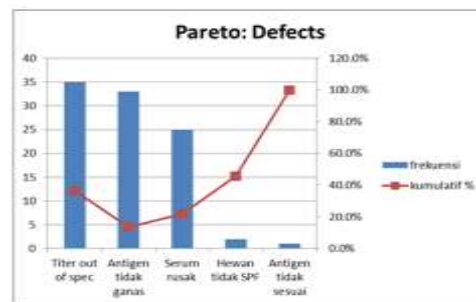
(Source: Own data processing)

(Figure 4.15 Pareto diagram of *safety test* with frequency values)



(Source: Own data processing)

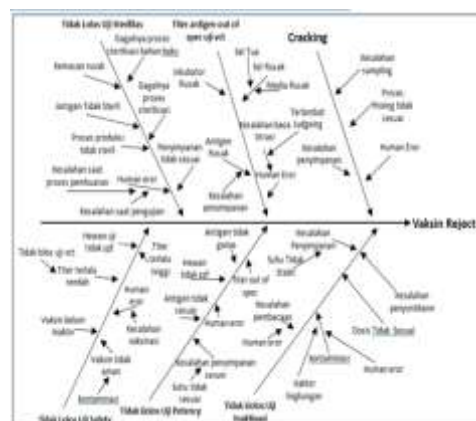
(Figure 4.16 Pareto diagram of the *Potential test* with cumulative frequency values)



(Source: Own data processing)

(Figure 4.17 Pareto diagram of *Potential* test with frequency values)

Furthermore, it can be used as a reference in finding solutions to problems that have been described by the Pareto diagram as in the previous discussion. From the Pareto diagram that has been made, it can be concluded that the antigen titer factor that is not standard or *out of spec* has the highest frequency value based on the Pareto diagram both in *safety testing* and *potency testing*, this can be examined as the cause of the high frequency of failure of safety-potency testing by outlining what factors cause this to happen, using a *fish bone diagram* as in **Figure 4.18** below:



(Source: Own data processing)

(Figure 4.18 Cause and Effect *Fish Bone* Diagram for *Safety-Potency Test*)

2. Measure Phase

Measurement is a key transition step in a *Six Sigma project* in this step the team will reformulate the problem and begin the search for root causes. This phase consists of 7 stages, namely:

- Selecting the Data to be Measured
- Creating an Operational Definition
- Identifying Data Sources
- Implement
- Calculate the six sigma levels for the overall process
- Calculate the six sigma level for the sub process
- Calculating *the Cost of Poor Quality*.

The following is antigen titration data conducted by the RnD research division obtained from the field as shown in **Table 4.6** below:

NO	SEED DATA	TITER	DAY	NO	SEED DATA	TITER	DAY
1	PC 48	7.5	5	31	PC68	6.5	5
2	PC49	7	5	32	PC66	5.75	5
3	PC50	7.25	5	33	PC67	6.25	5
4	ADN 90 P3	5.25	5	34	PC69	7	3
5	DNA 94 P3	0.75	5	35	PC70	7	5
6	DNA 94 P4	4.75	5	36	PC71	5.75	5
7	ADN 102 P3	1.5	5	37	ADN 028 PC06	1.5	5
8	ADN 89 P3	3.25	5	38	ADN 028 PC72	5.75	5
9	ADN 99 P3	6	5	39	ADN 028 PC 71	5.75	5
10	PC 51	6.25	5	40	ADN 028 PC73	4.5	3
11	PC 52	6.5	5	41	ADN 028 PC 74	6.75	5
12	Adeno 032 p6	5.75	5	42	ADN 028 PC02 50X	4.5	5
13	adeno 028 pc03	3.5	5	43	PC 74	0.75	5
14	PC51	6.75	5	44	PC 75	4.75	3
15	PC52	6.5	5	45	PC 76	5.5	5
16	PC55	6.75	5	46	PC 77	5.75	5
17	PC56	2.5	5	47	PC 77	4.75	5
18	PC50	4.75	5	48	PC 78	6.75	5
19	PC57	4.5	5	49	ADN 032 P5 50X	5.75	5
20	PC59	6.5	5	50	PC 79	4.75	5
21	PC60	8.25	5	51	PC 80	6.5	4
22	Adeno 032 p6	5	5	52	PC 81	7	5
23	Adeno 037 p9	5	5	53	PC 82	7	4

24	Adeno 032 p6	4.5	5	54	PC 82 P7	6	5
25	ADN 037 50x	7.75	5	55	PC 84	5.75	5
26	PC65	7.5	4	56	PC 85	6.75	4
27	PC62	6.75	5	57	PC 86	6.25	5
28	PC63	4.25	5	58	PC 87	6.5	5
29	PC67	3.25	5	59	PC 88	5	5
30	PC65	4	4	60	PC 89	5.75	5
				61	PC 90	5.5	5

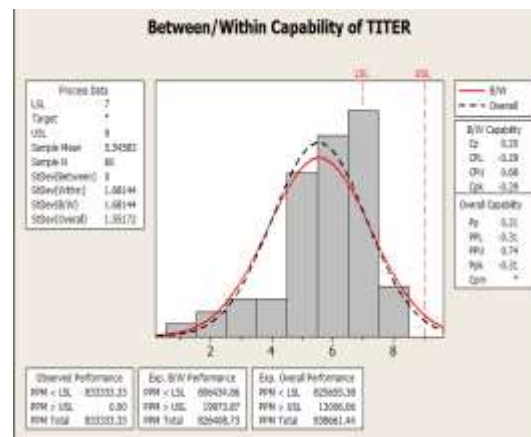
(Source: Own data processing)

(Table 4.6 seed and titer data)

From the data listed in 'Table 4.6 processed using the Minitab 15 application, the data obtained is as in Figure 4.19 below:

Calculating *Six Sigma Levels* For the Overall Process

Calculating *Six Sigma Levels* For Sub Processes



(Source: Definition of Process Capability)

(Figure 4.19 Display of AKP Results with the Minitab Portable Program)

Defect Per Million Opportunity (DPMO) is 826408.73. This value can be seen from the total PPM in Figure 4.19 , meaning that in one million processes carried out, there are 826408.73 defects, which is greater than the upper limit or USL, which is 9 DPMO and also higher than the lower limit or LSL, which is 7 DPMO.

From all the analysis conducted, it can be concluded that the entire process is still not running well and still requires improvement.

The manual calculation method for calculating DPMO (*defects per million opportunities*) can be seen in Figure 2.20 as follows:



(Source: Management Science)

(Figure 4.20 How to Calculate DPMO)

If calculated manually based on the same data as the calculation using the Minitab application as in **Figure 4.20** above, the results are as follows:

It is known:

Defect = 51

Units = 60

Opportunities = 1

Asked: what is the value of DPMO?

Solution: $(D/U \times O) \times 1000,000$

$(51 / 60 \times 1) \times 1000,000 = 850,000$

The value obtained from manual calculations is almost the same as the value obtained using the Minitab application, namely in the range of numbers > 800,000 DPMO .

3. *Analyze* Phase

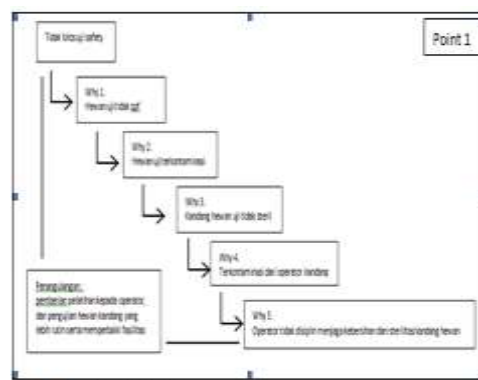
Analyze is the third stage of DMAIC. This stage aims to analyze the causes of the problem based on the highest priority. At this stage, the problem analysis can refer to the cause and effect diagram or *fishbone* that has been described in the *measure phase* .

fishbone diagram that has been described, it is known that the problem that occurred in the manufacture of the IBH vaccine was in the *Safety-Potency test* , and based on the Pareto diagram in Figure 4.16 and Figure 4.17, it is known that failing the *Safety-Potency test* is the main cause of the failure of the vaccine that was made, so that this makes research using the *Six Sigma method* prioritize the description of the problem in the *Safety-Potency test* , the following is a description of the problem in the *Safety-Potency test* which is described in Table 4.7.

Table 4.7 data on the causes of vaccines failing the test

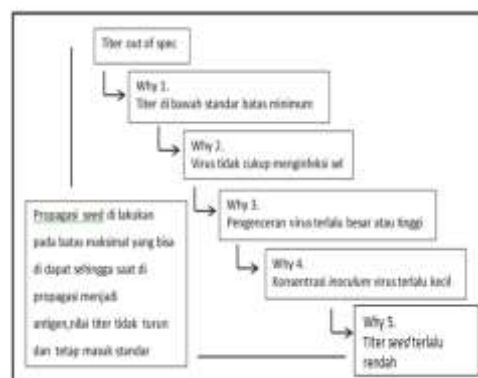
	Parameter uji safety	Parameter uji potency
Point 1	Hewan uji tidak SPF	Antigen tidak ganas
Point 2	Tidak lulus uji wt	Hewan tidak SPF
Point 3	Vaksin belum inaktif	Titer out of spec
Point 4	Vaksin tidak aman untuk hewan uji	Antigen tidak sesuai
Point 5	Kesalahan vaksinasi	Kesalahan penyimpanan serum
Point 6	Titer terlalu tinggi	-

(source : own processed data)



(Source: Own Data Processing)

Figure 4.21 diagram 5 why analysis



(Source: Own Data Processing)

(Figure 4.22 diagram 5 Why Analyze titer out of spec)

From Figure 4.22, it can be concluded that one of the factors that causes a vaccine to fail the test is an *out of spec titer* after being analyzed using the method. 5 why analysis results show that there are 5 main factors that cause *out of spec titers* , namely:

- Titer below the minimum limit standard
- Viruses do not infect enough cells

- c. Virus dilution is too large or high
- d. The concentration of the virus *inoculum* is too small
- e. *Seed titer* too low

Of the five factors above, the steps that can be taken are:

Seed propagation is carried out at the maximum limit that can be obtained so that when propagated into antigens, the titer value or virus concentration does not decrease and remains within the standard."

4. *Improve* Phase

In the *Improve* and *Control* phases in this study, only suggestions were given by the author because the problem limitation in the previous chapter 2 only conducted research and problem identification using the DMAIC method, until the *Analyze* phase .

In the *Improve* phase namely finding and identifying creative solutions to fix and prevent problems in the process. Use *brainstorming techniques* such as *six hats* or *random word* . Some projects can use more complex analysis tools such as DOE *Design Of Experiments* . The activities in the *improve* phase are as follows:

1. Creating innovative solutions
2. Focus on the simplest or easiest solution
3. Perform solution testing
4. Create a detailed *implementation plan*
5. Start making improvements.

And the suggestions that can be given by the author in this study based on the data that has been described in the previous phase of DMAIC are as follows:

- a. Counting cells during *shedding* on *roller bottles* so that virus incubation in cells can be maximized without experiencing cell damage that causes antigens to have to be *harvested* more quickly.
- b. Ensure the correct dilution calculation so that it can be standardized in each *seed dilution process* as antigen *inoculum* .
- c. *The harvested* antigen must be stored in proper storage while waiting for the time to be produced into a vaccine.
- d. Virus level testing or VCT titration on each post-harvest and pre-production sample to maintain the quality of the antigen produced.
- e. *Seed* propagation is carried out at the maximum limit that can be achieved so that when it is propagated into an antigen, the titer value or virus concentration does not decrease and remains within the standard.

5. *Control* Phase

Control phase in the DMAIC cycle is carried out to ensure continued success, therefore monitoring of the improvements made is needed, the method is to create a *control plan*, carry out monthly *updates* of process documentation, both business processes and production processes that have been supervised,

and make *training records* as needed, *control chat* can be used in this *control phase* , In addition there is an additional phase that is a supplement to the DMAIC phase, namely the *Replicate* or replication phase, this stage is the stage of replicating improvements that have been successfully carried out to be implemented in other processes this will encourage *knowledge sharing* between departments in the company to ensure the achievement of *operational excellence*.

6. Analysis and Discussion

From all the calculation results using the method *Failure Mode and Effect Analysis* (FMEA) to determine critical components of sewing machines that are easily damaged during the production process, namely needles, in calculating *rank* or value. RPN has a *rank* of 98 RPN, because the cause is. Inappropriate adjustment, often experiencing impact or friction on the rotary part , as a critical component because it has the largest percentage of *downtime* on the needle has 67.07%, thread has 21.59%, bobbin has 6.81%, lifeboat has 3.40%, and rotary has 1.1%, compared to other components . In the needle component, the results that have been set for the maintenance time on the needle for 1 day, the thread component for the maintenance time interval on the thread for 5 days, in the bobbin component the maintenance time on the bobbin is 12 days, in the lifeboat component the maintenance time on the lifeboat for 10 days, and at least requires the existence of *Condition Monitoring* .

CONCLUSION

1. Based on the research entitled “*Analysis of IBH Vaccine Product Quality Using the Six Sigma Method and DMAIC Approach at PT Vaksindo Satwa Nusantara*”, it can be concluded that the quality level of the IBH vaccine produced on a trial scale is still far from meeting acceptable quality standards. This is evidenced by the calculated DPMO (Defects Per Million Opportunities) value of 826,408.73, which indicates that out of every one million units produced, approximately 826,408 units are defective. This DPMO value falls below the first sigma level (690,000 DPMO), revealing that the existing production process operates with a sigma level of less than 1 and a yield performance below 30.9%. The primary contributor to product defects, as identified through the Pareto diagram, is the “out of specification” antigen titer, which accounts for 70% of all recorded defects, or 30 out of 80 total defect cases. This is corroborated by the low average process capability value (mean = 5.54583), which is below the acceptable standard for antigen titers. To address this quality issue, the company must optimize the seed virus propagation process to ensure that the resulting antigen retains sufficient virus concentration. This includes standardizing the dilution process, accurately calculating inoculum volumes, and implementing rigorous virus content testing (e.g., VCT titration) both after harvest and before production. Such corrective actions are critical to ensuring that each batch of IBH vaccine consistently meets predefined quality standards. By applying these improvements within the Six Sigma DMAIC framework, PT Vaksindo can significantly reduce defect rates, enhance product consistency, and strengthen its commitment to producing high-quality veterinary vaccines.

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