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Deviation Handling Model in Highly Regulated Industry (Study case: PT XYZ)

Ahmad Senjaya[1], Arief Daryanto[2], Setiadi Djohar[3]

[1, 2, 3]School of Business, Bogor Agricultural University (IPB), Jl. Raya Pajajaran Bogor, Indonesia 16151, Indonesia

Abstract: ***This study aims to develop an effective and efficient deviation handling model that used in the pharmaceutical industry (case study at PT XYZ). The AHP method is used to analyze the priority of deviation categories, which is used as the pilot for modelling. The period of data analyzed is data deviation of 2015 and 2016. Analysis of important factors in handling deviations is analyzed through in-depth interviews with stakeholders (Production manager, QA Manager and Head Quality). The AHP analysis identifies eight categories of deviations that are prioritized in construct a deviation handling model. The deviation handling model has been verified to provide more effective and efficient results in addressing the risks involved in an aberration.***

Keywords: Pharmaceutical industry, AHP, risk management, deviation handling model

1. Introduction

Indonesia is big market for pharmaceutical industries. Populations of Indonesia increasingly year by year, in 2020 total populations of Indonesia predicted would be 254 million with 52 % productive population by 132 million (UNDP, 2010). Market share of Indonesia's pharmaceutical industries in 2015 is 62 trillion rupiah, increasing 11% from the previous year. Indonesia's pharmaceutical industries in 2025 predicted would reach 800 trillion rupiah and being the 15th largest in the world with annual optimistic growth by 20%. This great potential market has an investment value of 215 trillion rupiah, which will create 2 million job opportunities in pharmaceutical sector by 2025 (Setiawan, 2016). Implementation of Jaminan Kesehatan Nasional (JKN) which stipulates that all citizen of Indonesia should be a member of BPJS by 1 January 2019 at the latest (BPJS, 2016), is a driver of growth of the pharmaceutical industry.

The supply chain of Indonesian pharmaceutical industry from upstream to downstream consist of suppliers, manufacturers, distributors/wholesalers (PBF), retailers, and customers (Knoop, 1998). Half of the overall risk of pharmaceutical supply chain is derived from internal risks that possibly controlled by the company (Jaberidoost, 2015).

The phases of drug products manufacture consist of various interrelated activities, such as material acceptance, material storage, drug manufacturing, drug packaging, storage of finished product and drug distribution. Throughout the process of drug manufacture there is possibility of nonconformance/deviation against the predefined requirements. Deviations can be detected in all phases of manufacture of drugs or in quality control activities.

Management is mandatory to take decisions properly on the quality of drug products in case of deviation in the drug product manufacture process. Decisions on status of drug products are divided into three, i.e. the product is released, the product is rejected, or the product is quarantine because it requires further investigation.

Strictly excessive management decisions on product status has a business risk, where the actual drug product remain good in quality yet decided to be rejected and the products must be destroyed. It will be consequent on increasing of production cost due to production failure, and it certainly has an impact on business sustainability of the company.

Hesitant management decision on product status lead the company to take more time in determining the status of the drug product, consequently the product must be quarantined for a while until a decision is made on the status of the drug product. Delays in drug product status potentially increase production cost due to increase product storage time, further effect of delayed supply of drug products to the market. Modern quality management system measure the company's ability to supply quality products in timely manner to customer (Customer Service Level) becomes one of the key performance indicators of the company (ICH, 2009), especially for live saving products where unavailability of marketable products may threaten patient safety.

Excessive tolerance management decision on product status has a risk of drug products that are not accordance with quality standards and potentially cause complaints, was decided to be passed and distributed to the market, consequently impact on health and safety of patients and the company should withdraw from the market.

The Indonesian and international pharmaceutical authorities only provide general operational guidance (guidelines) on Good Manufacturing Practices (GMP/CPOB), technical guidelines for application of GMP and quality risk management. Based on the above explanation, the authors are interested to conducting research on the decision making process of the technical handling of deviation in production area of pharmaceutical industry, which currently the technical handling of deviations vary depending on the competence and experience (expertise) of personnel.

The pharmaceutical industry has a standard process capability value of 2-3 sigma, which means it only allows 308,58 defect in one million products (Martin, 2011). Process capability with value of 2-3 sigma will impact to total cost of quality equal to 20-25% (Hussain, 2005). The

total loss due to small error in the investigation is 72% worth <$ 10.000 and 28% worth $10.000 - $100.000. Total losses due to a complex investigation error are 35% worth <$ 100.000, 52% worth $100.000 - $500.000 and 13% worth $500.000 - $ 1.000.000. The production process in the pharmaceutical industry is not free from problem/deviation, there are inherent risks due to poor process capability or inadequate quality system implementation.

XYZ is one of the MNCs in Indonesia engaged in the pharmaceutical industry. XYZ handles deviations in the production area referring to guidelines issued by relevant authority bodies and based on the competencies and experience of the personnel involved. Different competencies and experiences of personnel result in differences in the handling of deviations in the production area, potentially disproportionate (strictly excessive or excessive tolerance). Based on the above problems, this study aims to:

1) Identify the types of deviations with major and critical category that may occur in the process of making pharmaceutical products.
2) Analyse priorities of deviations by major and critical category that may occur in the process of pharmaceutical products.
3) Analyse priority deviation impact to patient, product quality, validation status and qualification status.

Analyze the important factors into consideration in determining the status of the products. The scope of this study was limited to the process of handling XYZs deviation in non-sterile drug production process (from weighing of raw materials until finished products sent to warehouse) with major and critical severity.

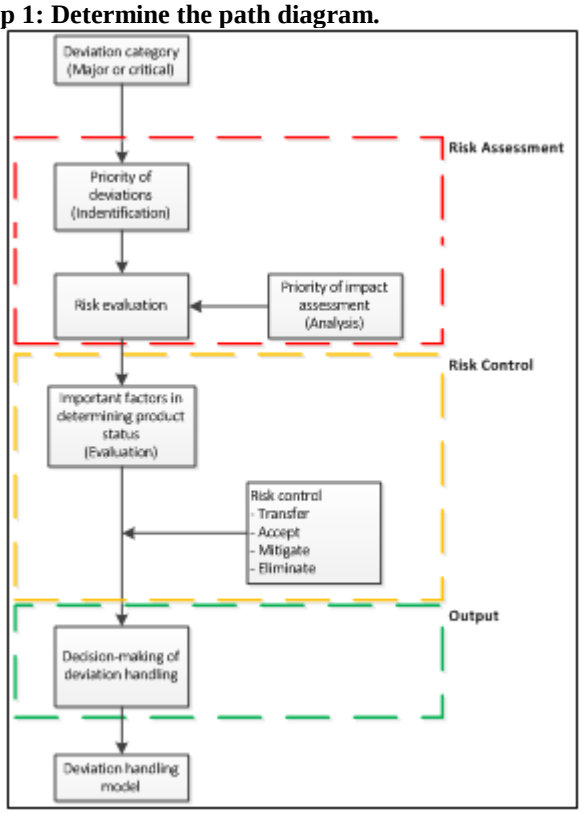
2. Data

The research used primary data collection technique through processing of retrospective deviation data, filling questionnaire and interview with the respondent chosen by purposive sampling. Criteria of respondents in this study are stakeholders in handling of deviation in XYZ and has experienced in the pharmaceutical industry at least 10 years. Based on above criteria, author identified three respondents namely one person of production manager and two of person Quality Manager.

3. Methodology

The research method used is descriptive qualitative with retrospective data collection technique and in-depth interview about handling deviations that occur in the XYZ's production process. Path analysis in this study through the stages:

Step 1: Determine the path diagram.



Picture 1 Path Diagram

Step 2: Determine the risk category of deviation

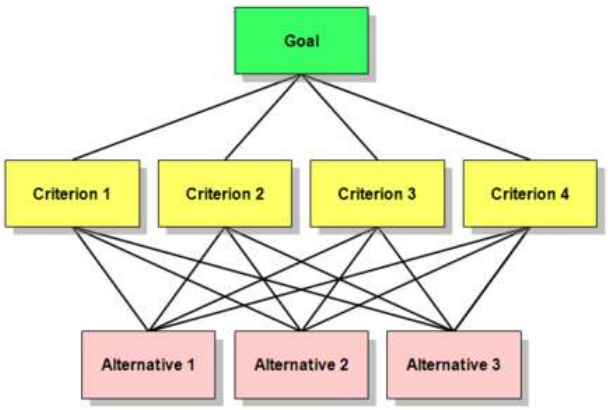
Processing of retrospective data is performed in the previous two years (2015 - 2016). The data obtained is categorized based on the same risk by interview with stakeholders (Quality Manager).

Step 3: Perform AHP

AHP was developed by Saaty in 1997, which is one of decision making methods to establish priority of alternative when there are many criteria to consider. This approach allows decision-makers to construct problems in a multilevel hierarchy consisting of objectives, criteria and alternatives (Liberatore & Nydick, 2007).

The main advantage of AHP is the use of pairwise comparisons to obtain scale-ratio measurements. Ratio scale is a natural way to compare between alternatives and allows measurement of tangible and intangible factors. AHP allows for inconsistencies in the assessment, however AHP takes measurements of whether inconsistencies in the assessment are made and sets an acceptable limit of tolerance.

AHP divides the problem into criteria according to the nature and purpose of the problem. AHP divides factors in the target hierarchical schemes according to the relationship between factors. The hierarchical standard can be further divided to form a hierarchical structure model (as shown in figure 2) which can be analyzed quantitatively and qualitatively to obtain the weights of importance of the lowest hierarchy criteria against the highest hierarchy criteria. AHP fins the final synthesis weights through pairwise comparisons to get objective and accurate results (Xi & Qin, 2013).



Picture 2 Path Diagram

Shashank et al (2016) explains the steps of the AHP method are as follows:

Make a pairwise matrix comparison.

$$A = \begin{bmatrix} a11 & a12 & \cdots & a1n \\ a21 & a22 & \cdots & a2n \\ \vdots & \vdots & \ddots & \vdots \\ an1 & an2 & \cdots & ann \end{bmatrix}$$

n is the order of the matrix A.

Normalize the matrix A.

$$A = \begin{bmatrix} a'11 & a'12 & \cdots & a'1n \\ a'21 & a'22 & \cdots & a'2n \\ \vdots & \vdots & \ddots & \vdots \\ a'n1 & a'n2 & \cdots & a'nn \end{bmatrix}$$ and $a'_{ij} = \frac{aij}{\sum_{i=1}^{n} aij}$, where ij: 1, 2, 3, …, n

a'_{ij} = The normalized value of pairwise comparison row i and column j.

a_{ij} = Pairwise comparison value row i and column j.

$\sum_{i=1}^{n} aij$ = Number of pairwise comparison value from row 1 until n in column j.

Normalization is performs by dividing the value of the matrix component by the sum of column value.

Calculation of eigen value and eigen vector.

The eigen value is obtained by multiplying the matrix A with the criterion vector (W).

$$W = \begin{bmatrix} W1 \\ W2 \\ \vdots \\ Wn \end{bmatrix}, \quad W_i = \frac{\sum_{i=1}^{n} a'ij}{n} \quad \text{and} \quad W' = A.W = \begin{bmatrix} W'1 \\ W'2 \\ \vdots \\ W'n \end{bmatrix}$$

$$\lambda \max = \frac{1}{n}\left(\frac{W'1}{W1} + \frac{W'2}{W2} + \cdots + \frac{W'n}{Wn}\right)$$

W = Eigen vector.

Wi= Eigen value of matrix A (mean value of rows of the normalization matrix A).

W'= Multiplication of matrix A with eigen vector.

λ max = The largest eigen values of pairwise comparison matrix.

Consistency check

Consistency index (CI) = $\frac{\lambda \max - n}{n-1}$

Consistency ratio (CR) = $\frac{CI}{Random\ index\ (RI)}$

n = Number of comparable criteria.

If CI = 0, then decision making consider as consistent. If it is not fully consistent then acceptable level of consistency is determined by comparing CI to random index (random index) as mention in table below.

Table 1: Random index and recommendation of CR consistency ratio.

N	3	4	5	6	7	8
RI	0,52	0,89	1,11	1,25	1,35	1,4
CR value*	<0,05	<0,08	<0,10	<0,10	<0,10	<0,10

* = Recommended

n = Number of comparable criteria.

Computation of global priority score.

The local weighting of each criterion is determined by obtaining the eigen vector and the vector value of each pairwise comparison, with the CR value corresponding to the recommendation.

GPSij = $\sum(CWij\ X\ GWc\ ij)$

GPSij = Global priority scores of alternatives.
CWij = Local weight of alternatives with respect to criteria.
GWc ij= Global weighting of criteria.

Step 4: Determine the important factors

In-depth interview are conducted face-to-face, referring to risk evaluation results. Use of voice recorder during the interview is tailored to the convenience of respondents. Output of the in-depth interview is to get important factors that need to considered in determining the status of the product and controlling the risks. Stakeholder in the in-depth interview is Quality Manager, which play an important role in handling deviations in the production process.

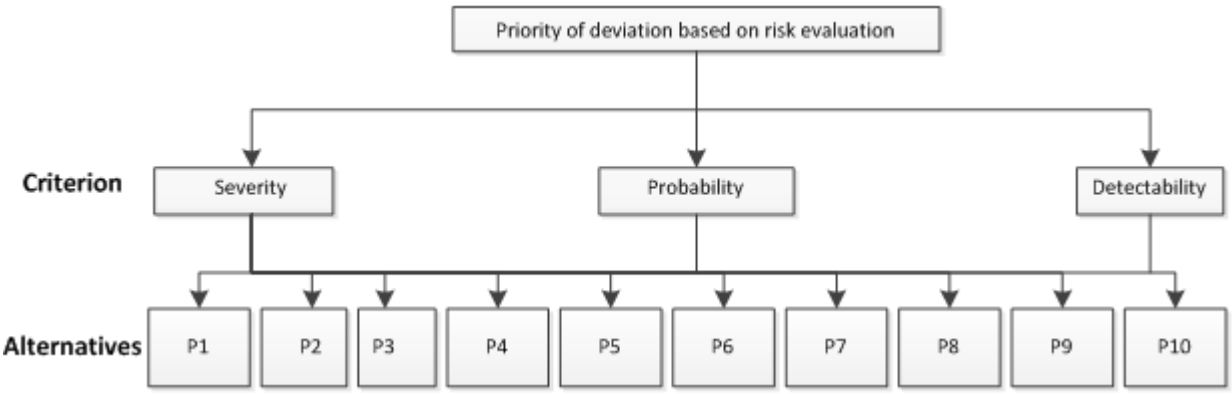
Step 5: Constructing the model and verification

Deviation handling model is construct from AHP analysis and the important factors. Verification of the decision-making model is performed by using the model that has been made, as a guide in handling deviations in cases of previous deviations.

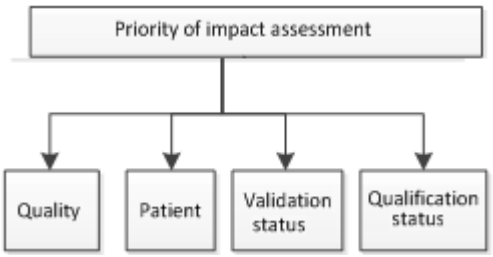
The concept of AHP used to dig information about:

- Stipulates priority of deviation category based on risk level.
- Stipulates priority of deviation impacts.

Hierarchical structure is mention in picture 3 and picture 4.



Picture 3 Hierarchical structure of priority of deviation



Picture 4 Hierarchical structure of impact assessment

4. Empirical Results

Analysis of XYZ deviation data

Deviation data are used to determine risks that have occurred during the last two years (2015 and 2016) in the XYZ. Some of deviations sometimes have the same risk, therefore in the handling of deviation could be categorized into one deviation category. Deviation data are categorized based on the similarity of risk into deviation category. Categorization of deviation is performed to ease the creation of deviation handling model.

The process of categorization of deviation data is performed through an in-depth interview with Head of Quality which is stakeholder in determining the deviation category in the process of deviation handling. The Head of Quality has more than 15 years experiences in pharmaceutical Industry with expertise in Quality Assurance, Quality System, Quality Control, Validation, Production, Registration, Quality Risk Management and Computer System Validation.

Period of data used is 2 years, because in the last 2 years in XYZ has been a lot of updating machines, systems and supporting facilities in the production area. Deviation data of 2015 backward is considered irrelevant as a pilot because it is not prospective and representative. The deviation handling model is designed to adapt to the current condition of XYZ and prospectively handle future aberrations. In-depth interview concluded that from 10 categories of deviation there are 8 categories of deviation that can be used as a pilot in creating a deviation handling model, as describe in the table below:

Table 2: List of deviation category

No	Deviation category
P1.	Particles contamination.
P2.	Out of specification (OOS) assay and degradant.
P3.	Out of specification (OOS) preservative content.
P4.	Out of specification (OOS) in process control parameter of bulk.
P5.	Critical parameter process has not been validated.
P6.	Loss of component (excipient or intermediate).
P7.	*Major/critical defect* in packaging process.
P8.	*Major defect* of bulk.

Microbial contamination and cross-contamination are excluded from deviation category because the category cannot be tolerated due to its risk which difficult to mitigate. Deviation of microbial contamination and cross-contamination should be treated by localization and destroy the impacted batch.

Priority deviation category analysis based on risk evaluation

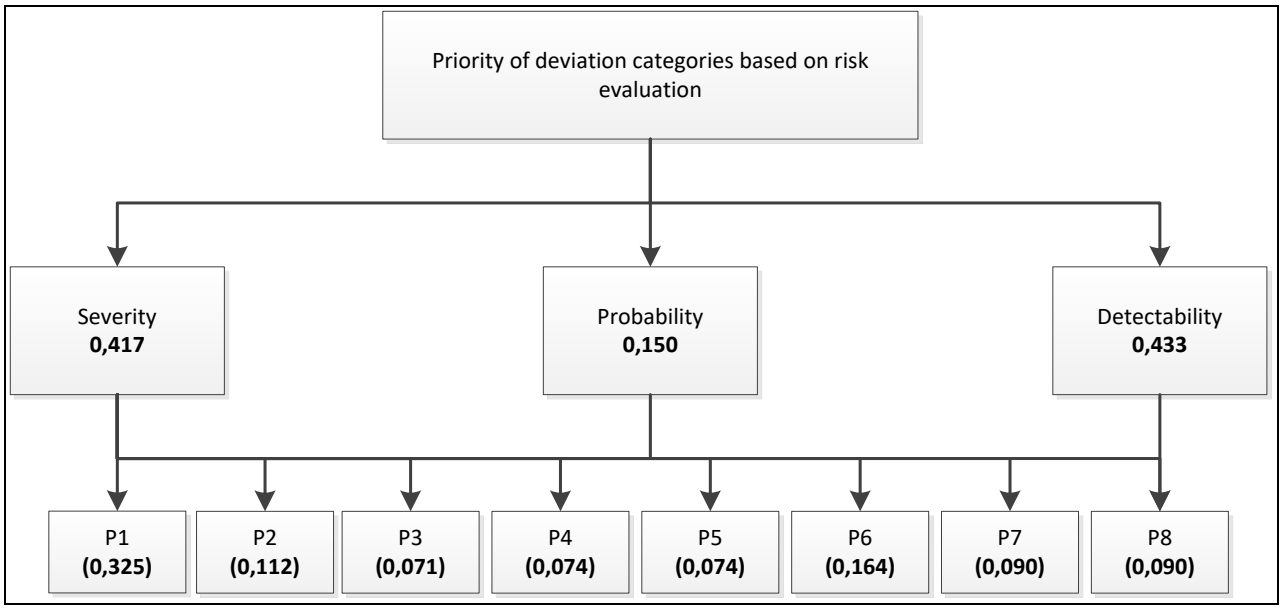
The process of prioritizing the deviation categories is performed using the AHP method with the criteria (severity, probability and detectability). An alternative to the criteria is the deviation category obtained from in-depth interview with Head of Quality. The selection of criteria is based on risk analysis, where risk is a combination of severity and probability (ISO/EIS Guide 51, 2014). XYZ implement risk management by adding the detectability factor as a correction to probability. Detectability also describes the ability of the system owned by XYZ in detecting the occurrence of deviation.

AHP analysis is performed by distributing questionnaires to stakeholders involved in decision making on handling of deviation in XYZ. The stakeholders are Production Manager, Quality Assurance Manager and Head of Quality. All stakeholders have experience in pharmaceutical industry for more than 10 years.

Based on AHP analysis, detectability (0,433) is the most important criterion in determining the priority of deviation categories followed by severity (0,417) and probability (0,150). Stakeholders are more concerned with the ability of the system to detect deviation and severity in evaluating the risk of deviation than the frequency of the occurrence (probability). Weighing of severity-probability-detectability

factors derived from AHP analysis can also be used in preparing risk management using FMEA (Failure Mode Effects Analysis) method in XYZ. FMEA method applied by XYZ has not determined the weight of severity-probability-detectability factors. These factors cannot be generalized to have the same weight, each of them has a different level of importance and it will enhance accuracy in evaluating the risk of deviation.

Deviations that have the same global priority score will be sorted according to the sequence of stages of production process. The earlier stages have lower risk than the final process stages. The priority of deviation category consecutively become P1 (0,325) > P6 (0,164) > P2 (0,112) > P8 (0,090) > P7 (0,090) > P4 (0,074) > P5 (0,074) > P3 (0,071). The consistency level of the AHP analysis result is 0,05 (satisfactory consistency level is <0,10), it can be concluded that the AHP results are consistent and can be used in constructing the model. Priority deviations indicate the sequence of deviation risk level from the highest risk level (P1) to the lowest risk level (P3). Preparation of deviation handling model follows priority order based on risk evaluation of deviation. The results of AHP analysis of deviation category priority based on risk evaluation are described in the figure below.



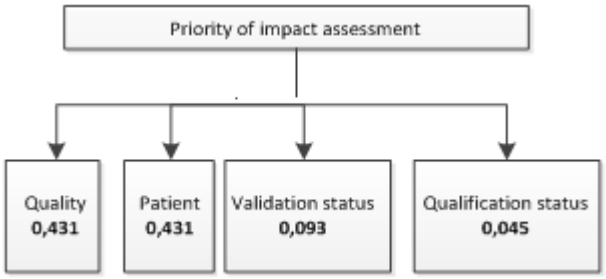
Picture 5 AHP structure of priority of deviation

Priority impact assessment analysis of deviations

Impact on product quality means all risks that can affect the fulfillment of product specifications based on documents registered to BPOM. Impact on patient means any risk that may affect the safety and security of the patient. Impact on validation status means any risk that may affect the validity of the process validation status. Impact on qualification status means any risk that may affect the validity of qualification status of tools/systems.

Prioritizing the impact assessment of deviations is carried out using the AHP method with predetermined criteria (impact on quality, patient, validation status and qualification status). The selection of criteria is based on common practices in handling deviations in XYZ, but in general the importance level (risk weight) of deviation impact has not been established. Determining the priority of deviation impact will ease the determination of any risks that need to be considered in advance of deviation handling.

Respondents consisting of Production Manager, QA Manager and Head of Quality, assessed that the product quality impact (0,431) and patient (0,431) impact was the most important deviation impact in deviation handling. The third and fourth sequence respectively were validation status impact (0,093) and qualification status impact (0,045). The consistency level of resulting AHP analysis is 0,00 (the satisfactory consistency level is <0,10), it can be concluded that AHP results are consistent and can be used in modelling.



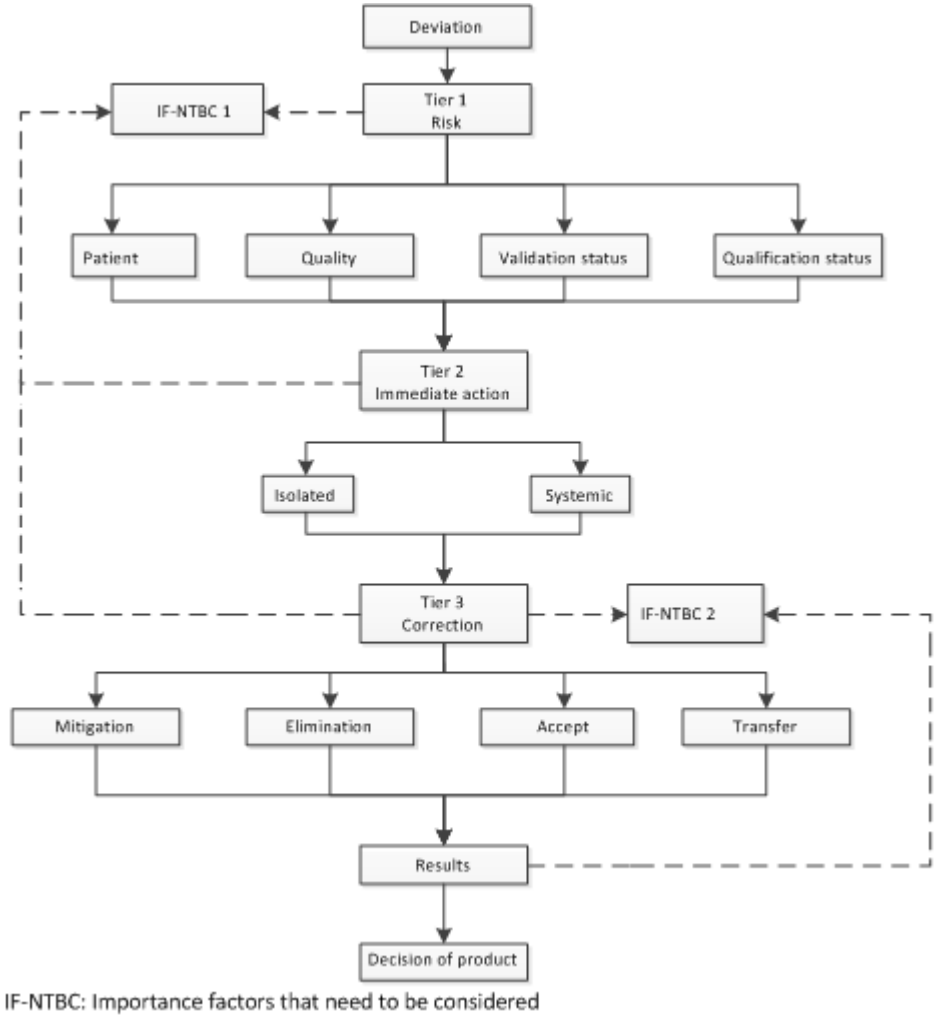
Picture 6 AHP structure of priority of impact assessment

Analysis of important factors in determining product status and risk control

Indepth interviews were conducted with a single respondent, Head of Quality, aiming to establish important factors in determining product status and risk control. The selection of single respondents is based on qualifications of experience and expertise possessed by the Head of Quality, this can be seen from the excellent consistency of Head of Quality in determining the importance of the variables compared to the AHP analysis against the Production Manager and QA Manager. Head of Quality as the person responsible for determining the status of the products, plays a very important

role in deciding the actions (immediate action and correction) to control the risk.

The risk of deviation is the first thing to consider in deviation handling. Knowledge of risk may affect risk control actions and product status decision determinations. The risks of deviations have an impact (consecutively) on the patient, product quality, validation status and qualification status. In understanding the risk of deviation, it should consider the IF-NTBC 1 (Important Factors Need to Be Considered 1). Immediate action and correction should refer to IF-NTBC 1. There are two immediate actions must be performed that is localized the impacted batch to prevent the spread of risk and determine whether the deviation is isolated or systemic. Determination of deviation is isolated or systemic will affect the correction to be taken. Proper immediate action and correction can prevent the spread of risk that will exacerbate the impact of deviations and threaten the status of product release. Risk control strategies are implemented with alternatives mitigation (reducing risk to acceptable risk), elimination (eliminate the risk), accept (accept the risk with appropriate and acceptable justification) and transfer (transferring the risk to third parties on business view). The success parameter of correction should be defined as IF-NTBC 2, the results of correction should refer IF-NTBC 2. Decisions of product status shall be based on the conformity of correction result made to IF-NTBC 2, if the results do not meet IF-NTBC 2 then the product cannot be released. The deviation handling model is simply explained in picture below.



Picture 7: Deviation handling model

Table 3: Detail of deviation handling model

No	Deviation category	Tier 1 (Risk)	IF-NTBC 1	Tier 2 Immediate action	Tier 3 Correction/strategy	IF-NTBC 2
1	Particles contamination.	1.Impact on patient safety 2.Impact on quality of product	1. Intrinsic. a. Commonly present in the raw materials (refers to hand book of excipient or excipient manufacturing process). -The impact on cosmetic defects. 2. Extrinsic. Other materials outside of the formula, so interaction with material in the formula is unkown: -Metal (refer to allowable limit). -Glass (zero tolerance). -Insect (allergen-zero tolerance). a. Acceptance limit. -Foodgrade. -GRAS (General Recognize As Safe), not foodgrade but there's safe limit. -LD50. -Daily intake. b. Detectability. -Visual. -Sensor (detection system). 3. Possibility to localized. -Physical properties. -Chemical properties.	1. Localization 2. Impact assessment (isolated or systemic) 3. Reconciliation of particle if required	Isolated: 1. Sortir 100% (manual or visual detection system). 2. PDE. 3. Reject impacted lot. Systemic: 1. Sortir 100% (manual or visual detection system). 2. PDE. 3. Reject the impacted batch. 4. Hold production of next batch.	1. Patient safety assessment -Acceptance limit of contaminant for the patient. 2. Quality assessment -The impact to bulk charateristics (particle size distribution). -PDE results of particle contamination. 3. Pharmaceutical assessment should be available.
2	Loss of component (excipient or intermediate).	1.Impact on patient safety 2.Impact on quality of product 3.Impact on validation status	1. Stage of process. a. Solid technology. -The Impact to drug dissolution. -The Impact to particle size distribution (PSD). -The Impact to homogenity. -The Impact to content uniformity b. Semisolid or liquid technology -The Impact to API solubility. -The Impact to bulk characteristic (density, pH, viscosity, organoleptic). 2. Amount of losses (refer to allowable limit by Authority). 3. Content per formula (refer to registration document). 4. Possibilty to localized.	1. Localization. 2. Impact assessment (isolated or systemic). 3. Reconciliation of losses component if it applicable.	Isolated: 1. Material adjustment. 2. Additional of two batch validation. 3. Reject the impacted lot. Systemic: -Reject the impacted batch. -Hold production of next batch.	1. Patient safety assessment -Assay of API 2. Quality assessment a. Solid technology -Drug dissolution, PSD, homogenity, and content uniformity. b. Semisolid or liquid -Assay of API and bulk characterization. 3. Validation assessment. 4. Pharmaceutical assessment should be available.

No	Deviation category	Tier 1 (Risk)	IF-NTBC 1	Tier 2 Immediate action	Tier 3 Correction/strategy	IF-NTBC 2
3	OOS assay and degradant.	1.Impact on patient safety 2.Impact on quality of product 3.Impact on validation status	1. Toxicology study of degradants. -Daily intake. -Acceptance limit. 2. Dossage form. a. Solid dossage form. -The Impact to homogenity. -The Impact to content uniformity. b. Liquid dossage form. -can not be localized. c. Semisolid dossage form. -The Impact to homogenity. 3. Stability study of assay and degradants. 4. Possibility to localized. -Liquid dosage form is not recommended. -OOS of degradants content can not be localized.	1. Localization. 2. Impact assessment (isolated or systemic).	Isolated: 1. Reject the impacted lot. Systemic: 1. Reject the impacted batch. 2. Hold production of next batch.	1. Patient safety assessment -Acceptance limit of degradants for the patient -Assay of API 2. Quality assessment a. Solid technology -Homogenity, and content uniformity. b. Liquid technology -Not aplicable. C. Semisolid technology -Homogenity 3. Validation assessment. 4. Stability assessment -Shelf life projection of impacted batch 5. Pharmaceutical assessment should be available.
4	Major or critical defect in packaging process.	1.Impact on patient safety 2.Impact on quality of product 3.Impact on validation status	1. Acceptance quality limit of defect. 2. The impact to critical quality attribut. 3. Possibility to localized. 4. Possibility to reprocess. -Only for solid dosage form. -Liquid and semisolid dosage form is not recommended	1. Localization 2. Impact assessment (isolated or systemic)	Isolated: 1. Sortir 100% (if aplicable). 2. PDE. 3. Reject the impacted lot. 4. Reprocess. Systemic: 1. Sortir 100% (if aplicable). 2. PDE 3. Reject the impacted batch. 4. Hold production of next batch.	1. Patient safety assessment -The impact to efficacy 2. Quality assessment -PDE results of impacted batch 3. Validation assessment 4. Pharmaceutical assessment should be available
5	Major defect of bulk (reduce usability).	1.Impact on patient safety (reduce efficacy) 2.Impact on quality of product 3.Impact on validation status	1. Acceptance quality limit of defect. 2. The impact to critical quality attribut. 3. Possibility to localized.	1. Localization 2. Impact assessment (isolated or systemic)	Isolated: 1. Sortir 100% (if aplicable). 2. PDE. 3. Reject the impacted lot. 4. Mitigation action (case by case). Systemic: 1. Sortir 100% (if aplicable). 2. PDE. 3. Reject the impacted batch. 4. Hold production of next batch.	1. Patient safety assessment -The impact to efficacy 2. Quality assessment -PDE results of impacted batch 3. Validation assessment 4. Pharmaceutical assessment should be available

No	Deviation category	Tier 1 (Risk)	IF-NTBC 1	Tier 2 Immediate action	Tier 3 Correction/strategy	IF-NTBC 2
6	OOS in process control parameter of bulk.	1.Impact on patient safety 2.Impact on quality of product 3.Impact on validation status	1. The impact to critical quality attribut. 2. Compliances with registration document. 3. Compliances with compendial. 4. Possibility to modify the process (based on scientific judgement). -Verification with sampling refer to validation study. 5. Possibility to localized.	1. Localization 2. Impact assessment (isolated or systemic)	Isolated: 1. Reject the impacted lot. 2. Process modification. Systemic: 1. Reject the impacted batch. 2. Hold production of next batch.	1. Patient safety assessment. -The impact to efficacy. 2. Quality assessment. -Verification of process modification with sampling refer to validation study. 3. Pharmaceutical assessment should be available.
7	Critical parameter of process has not been validated.	1.Impact on quality of product 2.Impact on validation status	1. The impact to critical quality attribut. 2. Compliances with registration document. 3. Compliances with compendial. 4. Possibility to modify the process (based on scientific judgement). -Verification with sampling refer to validation study. 5. Possibility to localized.	1. Localization 2. Impact assessment (isolated or systemic)	Isolated: 1. Reject the impacted lot. 2. Process modification. Systemic: 1. Reject the impacted batch. 2. Hold production of next batch.	1. Patient safety assessment. -The impact to efficacy. 2. Quality assessment. -Verification of process modification with sampling refer to validation study. 3. Pharmaceutical assessment should be available.
8	OOS preservative content.	1.Impact on patient safety 2.Impact on quality of product 3.Impact on validation status	1. Toxicology of preservative. -Daily intake. -Allowable limit. 2. Stability study of preservative. -Projection of preservative content at the end of shelf life. 3. PET test. -Refer to preservative content at the end of shelf life. 4.Possibility to localized.	1. Localization 2. Impact assessment (isolated or systemic)	Isolated: 1. Reject the impacted lot 2. Perform PET (refer to preservative content at the end of shelf life). Systemic: 1. Reject the impacted batch 2. Perform PET (refer to preservative content at the end of shelf life). 3. Hold production of next batch.	1. Patient safety assessment -Acceptable limit of preservative content. 2. Quality assessment -Results of PET. 3. Validation assessment. 4. Pharmaceutical assessment should be available.

Verification of deviation handling model

The verification of the deviation handling model is carried out on the handling of the previous deviation at XYZ, to ensure the model is fit and deliver results as expected. The deviations used in the model verification are the first priority deviation based on the risk evaluation of particle contamination. Handling deviations using the model shows more effective and more efficient results in dealing with the risks involved in a deviation.

5. Conclusion

The study identified eight categories of deviations that were used as pilots to construct the deviation handling model. The most priority deviation based on risk evaluation is particle contamination. Model verification has been performed on handling of deviation of particle contamination, the model proven to provide more effective and efficient decision-making.

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Author Profile

Ahmad Senjaya received the Apothecary degrees in Pharmaceutical Industry from University of Indonesia in 2012. He has experience in the pharmaceutical industry for almost 7 years. Start from 2014, he continue to study in School of Business Bogor Agricultural University, at Postgraduate Program of Business Management, focusing on majoring of strategic management.