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A new approach in identifying and evaluating quality risks in the pharmaceutical industry

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ABSTRACT

Background: Failure Mode and Effects Analysis (FMEA) is a highly structured and systematic technique for risk analysis, commonly used in all procedures of the pharmaceutical industry, from the design of the production facility and new product development to the product release. The important part of this method is the identification of risks and determining the risk priorities.

Methods: This study has been carried out in two steps: in the first step, all possible quality related risks have identified through literature review and interviews with experts of the pharmaceutical industry, subsequently these experts validated recognized risks. In the next step, the valid risks analyzed and evaluated through the combination of FMEA and Fuzzy TOPSIS methods.

Results: More than 100 main quality risks were identified in the pharmaceutical manufacturing companies. These risks originate from the redundant practices and processes of the industry. Consequently, twenty of the identified risks recognized as effective risks in the industry. Human errors in production, inadequate supervision on conduction of qualification of the production machineries, improper qualification in design and implementation of the heating, ventilation, and air-conditioning (HVAC) system, lack of standard procedures for handling of the non-conforming products, inadequate supervision on conduction of cleaning validation of the production facilities, and weakness in the documentation have been recognized as the most important risks in this study.

Conclusion: Risks survey results can point to the prominence of the quality assurance unit and its vital but partially neglected role in the generic pharmaceutical industry.

Keywords: Pharmaceutical Industry; Quality; Risk Identification; Risk Evaluation; FMEA; Fuzzy TOPSIS

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1. Introduction

"Medicines are of particular importance because they can save lives, improve health, and they promote trust and participation in health services" [1]. Pharmaceutical manufacturing industry has a vital role in fulfilling this goal, and patient access to medicines in required quantity, with permissible quality [2]. Not only Quality Assurance (QA) implementation contributes to the pharmaceutical industry, but also it impacts significantly every quality oriented manufacturing industry [3]. In the pharmaceutical manufacturing industry, every product and every process is associated with various risks. To maintain product quality throughout the product life cycle, a remarkable amount of time and resources need to be allocated. Risk is described in recent guidelines as a combination of the probability of occurrence of harm and the severity of that harm [4]. Quality risk management (QRM) is one of the most crucial tasks when it comes to the pharmaceutical industry since the industry produces medicines whose quality is directly related to the patient's health. International Conference on Harmonization (ICH) has developed various guidelines (i.e. ICH Q9) to protect the quality of medicines along with its safety and efficacy [5]. We take full advantage of the prevalent guidelines published by stringent authorities in the pharmaceutical industry, such as PIC/S, FDA, and ICH. With the advent of these guidelines in the pharmaceutical industry, we could foster our knowledge to improve the quality of medicines [6]. The current study tries to identify the quality related risks in the pharmaceutical manufacturing industry, analyze and evaluate the influential risks for better risk management strategies, by concomitant use of FMEA and Fuzzy TOPSIS techniques, which could be used as a guide in this industry [7]. This guide could be applicable even to the industry for the better control and management of quality risks or for the regulatory body as a checklist in their routine inspections.

2. Methods

Failure Mode and Effects Analysis (FMEA) is a systematic method for identifying failure modes of systems, processes, designs, services, and machineries. FMEA is widely used by corporations manufacturing products like pharmaceutical manufacturing industry, organizations, and firms to evaluate the effects of the failure modes. The goal of FMEA is to determine the reasons for the failure modes; thereafter it seeks to find ways to decrease or eradicate the possibility of these failures. The FMEA technique comes from the United States military procedure [8, 9]. The analysis is performed at the early operational stage of a system so that the removal or mitigation of the failure mode is identified, analyzed and evaluated as shown in the following equation [10]:

$$RPN = O \times S \times D$$

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Table 1. Scale of Severity (S), Occurrence (O), Detectability (D) and Grade of the Risks

Risk Severity (S)	**Meaning of the consequences of a failure**	**S coefficient**
Very insignificant	Failures and defects do not influence performance factors	1-2
Insignificant	Defects can be repaired and easily removed	3-4
Significant	Failures cause a gradual loss of structural safety and decrease of performance factors	5-6
Critical	Defects can cause ruptures and accidents	7-8
Catastrophic	Failure threatens the security (hazard to life and health) and is contrary to statutory regulations	9-10
Risk Probability (O)	**Meaning of the consequences of a failure**	**O coefficient**
Very low	Risk of the defect is unlikely, the probability is almost zero	1-2
Low	Very insignificant probability	3-4
Medium	The medium probability of defect	5-6
High	The construction complies with the projects, which faced with a lot of failures in the past	7-8
Very high	Very high Defects are inevitable	9-10
Risk Detectability (D)	**The probability of detecting inconsistencies based on provided control operations**	**D coefficient**
Very low	Emerging failures cannot be detected (no access or no opportunity to control)	10
Low	Detecting emerging failures is difficult/ technological checks are ineffective	8-9
Medium	Failures are difficult to detect during the control and test	6-7
Moderate	Moderate effect on product performance	4-5
High	Detecting failures is easy	2-3
Guaranteed	Failures, if occur, are explicitly recognized (the probability of detection >95%)	1

Grade of Risks	**Consequence**	**RPN**	**Acceptability**
Very High	Catastrophic	$RPN \geq 0.810$	Unacceptable
High	Critical	$0.392 \leq RPN < 0.810$	Undesirable
Medium	Significant	$0.150 \leq RPN < 0.392$	Moderate
Low	Low Significant	$0.036 \leq RPN < 0.150$	Acceptable
Very Low	Insignificant	$RPN < 0.036$	Acceptable

The multiplication of these factors leads to what is called Risk Priority Number (RPN) [11], where (S)-Coefficient is the severity of the failure, (O)-Coefficient is the probability of the failure, and (D)-Coefficient is the probability of not detecting the failure [12]. Quantitative estimation of O, S and D factors should be performed on a scale evaluation form for each of the factors separately. As per the evaluation coefficients, the hazard relation of Risk Priority Number (RPN) needs to be defined. We define these coefficients in Table 1 [13]. Grade of risks, risk's consequences, and acceptability, according to calculated RPN, are also shown in Table 1.

This study was carried out in two steps: in the first step, all possible quality related risks were identified through interviews with ten experts from the pharmaceutical industry. These qualified persons have had more than 15 years' experience in the quality system units of the pharmaceutical manufacturing companies. Then, all detected possible quality risks gathered as a list and circulated among experts for their final consideration to accept or reject new findings by justification. In the next step, the valid identified risks analyzed and evaluated through the combination of FMEA and Fuzzy TOPSIS methods in the context of Good Practices of the pharmaceutical industry (GXPs).

The Proposed Method of Fuzzy TOPSIS

A systematic approach to extending the TOPSIS method to the fuzzy environment is proposed in this section. This method is appropriate for solving the issue of group decision-making under the fuzzy environment [14]. In this paper, for linguistic variables, we consider the importance weights of various criteria and the ratings of qualitative criteria [15].

Ranking

In this stage, we propose a method of alternative ranking of the Coefficient Closeness (CC) or Risk Priority Number (RPN) that ratify each other.

A closeness coefficient defined to be able to determine the ranking order of all alternatives and select the best one from among a set of feasible alternatives. The closeness coefficient for each alternative then calculated as below:

$$CC_i = \frac{d_i^-}{d_i^+ + d_i^-}\ , i = 1,2,...,m \qquad \text{Eq. (01)}$$

Where d_i^+ denotes the distance between each alternative and ideal positive solution, d_i^- denotes the distance between each alternative and ideal negative solution [16].

$$d_i^+ = \sum d\left(\tilde{v}_{ij}, \tilde{v}_j^+\right) \qquad \text{Eq. (02)}$$

$$d_i^- = \sum d\left(\tilde{v}_{ij}, \tilde{v}_j^-\right) \qquad \text{Eq. (03)}$$

3. Results

In this study, we included ten experts, twenty effective risks, and three measures (O, S, and D). Here we assume that experts use the linguistic score set to assess the compatibility of each risk under each of the measure (criteria).

S = {VL, L, ML, M, MH, H, VH}, where VL (Very Low) = (0, 0, 0.1), L (Low) = (0, 0.1, 0.3), ML (Medium Low) = (0.1, 0.3, 0.5), M (Medium) = (0.3, 0.5, 0.7), MH (Medium High) = (0.5, 0.7, 0.9), H (High) = (0.7, 0.9, 1), VH (Very High) = (0.9, 1, 1)

In the phase one of this study, we encountered more than 100 main quality related risks. After analyzing and evaluating these recognized

Table 2. List of the identified effective risks

No.	Risks	Process
1	Improper design and implementation of Heating, Ventilation, and Air-Conditioning (HVAC) qualification	GEP*
2	Inappropriate formulation that results in the product quality and efficacy or increases production waste	R&D*
3	Failure to comply with rules, regulations, and standards of HSE	HSE*
4	Lack of SOPs and appropriate actions for nonconforming products, out of specification (OOS), and out of trend (OOT) cases	GLP*
5	The absence of a dedicated unit for quality control of hazardous products	GLP
6	Improper conduction of the product release process	QA*
7	Inadequate supervision on documentation, Standard Operating Procedures (SOPs), and Batch Processing Records (BPRs)	QA
8	Lack of Validation Master Plan (VMP)	QA
9	Absence or inadequate supervision on conduction of Cleaning Validation (CV)	QA
10	Absence or inadequate supervision on conduction of validation of the production process (PV)	QA
11	Absence or inadequate supervision on conduction of qualification of machinery and equipment	QA
12	Inadequate supervision or lack of Quality Risk Management (QRM) in the production of hazardous products	QA
13	Inefficient quality audit for suppliers of raw materials and active substances	QA
14	Inappropriate follow-up programs regarding corrective & preventive actions (CAPA) of deficiencies	QA
15	Human errors of production and packaging personnel	GMP*
16	Lack of assigning healthy personnel in production facilities with appropriate heath records	GMP
17	The absence of validated non- pharmacopoeia analysis methods for new molecules	GLP
18	Failure to select the appropriate packaging which preserves physicochemical properties of the medicine	R&D
19	Inappropriate sourcing of suitable raw material for the formulation of the new products	R&D
20	Lack of long-term stability studies according to standards of ICH guidelines	GLP

* GMP: Good Manufacturing Practices; GEP: Good Engineering Practices; R&D: Research & Development; QA: Quality Assurance; GLP: Good Laboratory Practices; HSE: Health, Safety, and Environment.

risks through the discussed methods in phase two, we found out that 20 of them can be assumed as effective quality related risks, and the other risks that account for more than 80% of total identified risks can be considered as ineffective quality related risks (acceptable risks). Identified risks were assigned to seven main processes and practices in the pharmaceutical industry (GXPs), including Good Manufacturing Practices (GMP); Good Laboratory Practices (GLP); Good Engineering Practices (GEP); Good Storage Practices (GSP); Health, Safety and Environment (HSE) related practices; Practices related to Quality Assurance (QA); and practices related to Research and Development (R&D). The list of twenty identified effective quality risks (alternatives) and their relevant processes in the pharmaceutical industry is shown in Table 2. The risks can be ranked as shown in Table 3.

4. Discussion

In our study, more than 100 main quality risks have been identified, from which more than 80% were expected to be acceptable with low or very low grade (ineffective risks), and only less than 20% of the total risks which account for 20 risks were assumed to be effective risks (moderate, undesirable, or unacceptable risks). We also found that about half of these effective risks (9 out of 20) related to QA processes. In the present study, it was also determined that the other 11 risks are related to 5 other processes, respectively: 4 risks related to R&D procedures, 3 risks related to GLP, 2 risks related to GMP, 1 risk related to GEP and finally 1 risk related to HSE practices. Within effective risks, no reported risk was due to GSP.

Among these 20 effective quality risks, the greatest number for the severity of risks (S), and the highest number for the occurrence of risks (O), in all seven processes were related to the Quality Assurance (QA) function. As for the detectability of risks (D), we found out that there is no significant difference between these seven processes.

In another survey which was done in the pharmaceutical industry in 2014 based on the cause and effect logic, in six main categories (6M) including Man, Material, Machinery, Method, Measurement and Milieu, it was also reported that the highest risks were related to quality assurance (QA) functions [17].

According to the data presented in Table 1 and Table 3, only one risk (R15) is unacceptable (catastrophic or with very high grade). This risk with the highest reported RPN related to GMP and human errors in the production of pharmaceuticals. Fourteen of the 20 effective risks (R1, R2, R3, R4, R5, R7, R8, R9, R10, R11, R12, R13, R14, R16) were assumed to be undesirable (critical or with high grade), and finally five of the 20 effective risks (R6, R17, R18, R19, R20) could be regarded as moderate (significant or with medium grade). Table 4 presents the summary of

Table 3. Ranking of the identified effective quality risks

Risks	d+	d-	CC (RPN)	Rank	Risks	d+	d-	CC (RPN)	Rank
R1	0.0294	0.0600	0.6710	3	**R11**	0.0292	0.0653	0.6912	2
R2	0.0415	0.0343	0.4523	14	**R12**	0.0581	0.0553	0.4876	12
R3	0.0478	0.0391	0.4496	15	**R13**	0.0538	0.0635	0.5414	9
R4	0.0313	0.0559	0.6412	4	**R14**	0.0378	0.0425	0.5293	10
R5	0.0458	0.0557	0.5484	8	**R15**	0.0220	0.0961	0.8133	1
R6	0.0536	0.0327	0.3791	17	**R16**	0.0419	0.0346	0.4524	13
R7	0.0327	0.0532	0.6192	6	**R17**	0.0480	0.0277	0.3661	18
R8	0.0450	0.0446	0.4979	11	**R18**	0.0624	0.0390	0.3844	16
R9	0.0319	0.0524	0.6221	5	**R19**	0.0656	0.0284	0.3019	19
R10	0.0302	0.0431	0.5881	7	**R20**	0.0824	0.0309	0.2725	20

the classification of the identified quality risks within the five main grades of the risks and relevant process in the pharmaceutical industry. Identified effective risks which account for about 20% of all recognized quality risks in the industry, can be easily used as a guide for the pharmaceutical industry for risk management and improvement of the quality of medicines. As per *Pareto* principle (the 80/20 rule), it could be assumed that about 80% of the undesirable effects (poor-quality medicines) come from 20% of the causes (effective risks).

5. Conclusion

The results of this study suggest that the FMEA method in combination with Fuzzy TOPSIS method could be used as a powerful tool for risk assessment in the pharmaceutical industry. The consequences of the ranking of effective risks can point to the prominence of the quality assurance function and its vital but partially neglected role in the pharmaceutical industry.

According to our findings, the pharmaceutical industry should exert more controls on personnel activities to reduce their unintended errors. Moreover, the industry should employ more measures regarding substantial improvements in QA activities such as qualification of systems and validation of processes, and more control and supervision on the documentation practices.

6. Conflict of Interests

The authors declare that they have no conflict of interests.

7. Acknowledgments

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