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Quality Risk Assessment Production of Beta Lactams by FMEA Model and Fuzzy Theory Method

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Abstract

Objectives: Quality risk assessment is one of the most important components of the quality assurance division in pharmaceutical industry.

To the best of our knowledge there is no previous study assessing risks and disruptions of the quality risk assessment in beta-lactam production in pharmaceutical companies. The lack o risk assessment may due to disrupt quality system, safety and efficiency of the product. The aim of this study was to evaluate the risk assessment in beta-lactam production in Iran considering process's priority, hazard and probability, severity and detectability of risks.

Methods: The study was carried out in 3 phases; risk identification through literature review, risk identification in Iranian pharmaceutical companies through interview with experts, risk analysis through a questionnaire and consultation with experts using group analytic hierarchy process Failure Mode Effects Analysis (FMEA) method and priority and risk evaluation of Fuzzy method in five Iranian pharmaceutical companies.

Results: According to the results, 109 main risks were identified in these pharmaceutical companies which could be divided in seven categories. The majority finding of the risks in this study were related to the quality control, quality assurance and manufacturing process. The manufacturing process and quality assurance were found to be the most important factor for consideration.

Conclusion: The results of the present study suggested that the FMEA method in conjunction with the supporting fuzzy set method can be effectively used for risk assessment in beta-lactam production and pharmaceutical industry. In this course, the risk assessment is the goal of this research. The use of this approach can support the project management team to establish corrective actions in quality system.

In future, we suppose to develop methods and strategy for the integration of different information Technologies and methods of analysis (FMEA). Also we will hope to reduction the risks, and Management stated strategy in companies.

Keywords: Pharmaceutical companies; Risk assessment; FMEA method; Fuzzy theory; Beta-lactam antibiotic

Introduction

The quality in the pharmaceutical industry has become a very important topic. Since the world has gathered together to harmonize its practices and guides and the launching of the FDA current good manufacturing practices – the cGMP; for the 21st century – there has been a growing awareness for the significance of the quality of the pharmaceutical products [1].

This awareness is represented through the appearance of several definitions defining exactly what the quality of the medicine should be [2].

Many articles were written to demonstrate the special nature of the product-customer relationship of medicine and patients [1]. Also the important role of governments was emphasized through the joint statement between the international pharmaceutical federation; FIP; and the international federation of pharmaceutical manufacturers associations; IFPMA; to ensure the safety of medicinal products in order to protect the patient [3], providing that the pharmaceutical industry is one of the most closely regulated industries for more than 50 years [1].

Since 2002, FDA began an initiative to address cGMP for the 21st century [1]. This effort involved taking new looks at both the regulatory and industrial systems for insuring drug quality [4]. Improving and promoting the quality of the product is the first and most important factor is to stay ahead of the competition and market share.

Today the concept of quality is developed and therefore, according to the rules of safe and effective health care system and pharmaceutical products for the final product is too important. Simply, if we want to express the newest and innovation, thus explained that:

Our study is the form of a computational approach using FMEA fuzzy theory in the field of quality risk assessment (QRA) Beta-lactam antibiotics on production in the pharmaceutical companies, and statistical methods such as mean; variance and standard deviation measure of the methodologies described can express the originality of their study.

Method

This study was carried out in three phases; risk identification through literature review (carried out on November2014), risk identification in five Iranian pharmaceutical companies. Through interview with experts, risk analysis through questionnaire, risk evaluation (carried

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out from November 2014untill May 2013).

In Phase 1, A literature review to identify pharmaceutical Risks; search engines, Scopus, PubMed, Web of Science and Google Scholar, was done for risk identification by several keywords; Risk assessment, quality system risk, risk management, Beta-lactam, pharmaceutical companies, pharmaceutical industry, Iran.

Risk identification in Iran pharmaceutical companies through expert opinion with an open questionnaire; for identifying pharmaceutical risks in Production of Beta-lactams in Iran, investigation risks through expert opinion was carried out. In this step, a group of 16 experts who had at least 5 years of experience in each of processes; such as quality control; quality assurance and manufacturing process management in pharmaceutical companies Management was selected to interview for risk identification.

It is trying to select experts from the companies that in field of beta-lactam production and field of work to cover all processes of view in the Iran's antibiotics pharmaceutical companies.

Before each interview, an introductory letter and open Questionnaire, which was validated in the pilot study, were sent to experts 1-2.5 hour interview with each expert was carried out and the questions related to risks and best practice for categorization of pharmaceutical Processes and functions were asked. After Coding and extracting risks from questionnaires, a summary of interview and identified risks were sent to interviewees for review and final confirmation.

In Phase 2, Risk analysis through a questionnaire and Interview with experts; all risks extracted from literature Review and expert interview (phase 1) collected in the other questionnaire for risk analysis. The questionnaire was designed in three factors in three parts; first part included severity; second one probability and the other on was detectability then the risk priority number can be obtained from the product of three factors; simultaneously by 0-10 rating scale.

A questionnaire was validated by 3 experts in the pilot study before sending a questionnaire to the experts. After sending questionnaires to the experts, an interview meeting was set with each expert to fill questionnaire in the face to face interview meeting. Except one, all questionnaires were responded by the expert team.

In Phase 3, Risk evaluation; risk evaluation was based on considering three factors. The priority was selected for scoring hazard of risks on processes after gathering the data, (fuzzy) method was applied for evaluation.

FMEA method

One of such methods is the analysis of the types and consequences of potential failures (Failure Mode and Effect Analysis - FMEA) [5,6]. To date, the FMEA-analysis is one of the tools to quantify risk coefficient.

Prediction of defects and failures, analysis of outcomes and prevention of their occurrence is the main objective of this method. The FMEA method allows identifying potential inconsistencies, their causes and consequences, assessing the risk of their occurrence and taking the measures to eliminate or reduce the probability of their occurrence. Reducing the risk and uncertainty of regulation for the probability of occurrence for the defect is the main goal of this method [7,8].

Fuzzy theory

As outlined in the previous section the key component of the approach presented in this paper are Fuzzy sets, introduced by Lotfi A. Zadeh [9]. They differ from the classical notion of set by allowing the gradual assessment of the membership of elements. This is described with the aid of a membership function valued in the real unit interval [0; 1]. Emerged from the development of the theory of fuzzy sets, the fuzzy logic is an extension of the case of multi-valued logic, assigning to each proposition a degree of truth - a value varying between1 (absolutely true) and 0 (absolutely false).

Defuzzicating fuzzy number

To become a fuzzy number to an exact amount of different methods such as center of gravity, most of the membership function, using left and right scoring fuzzy number and so on. Because this study due to the use of continuous membership function of the fuzzy number is used scoring method to right and left in this part of the procedure has been followed.

The exact total score obtained a fuzzy number of the left and right and the left and right points of the two special sets minimum and maximum fuzzy membership degree is obtained.

The two sets maximum and minimum, assuming that the fuzzy numbers [0, 1] is represented in the following (Figure 1).

The evaluate RPN in the method of FMEA by Fuzzy set

To create a model to calculate the risk priority queues forwarding and prioritization errors and their effects using fuzzy theory should be taken two major steps below:

1 Choose a fuzzy membership function

2 non-fuzzy membership functions

Choose a fuzzy membership function

For all the risk factors in the impact of the error , the probability of error detection probability of error of five linguistic variables very low, low , medium, high , very high used.

U)Reference Collection (Domain Change = [0, 1] (Figure 2)

Non-phase rate using (the left and right of the fuzzy number)

The method of using the non-fuzzy (Rate the left and right fuzzy number) we first non-fuzzy fuzzy numbers and a final rating is given to each fuzzy numbers.

Then we check FMEA Method.

Finally, according to Table 1, we can compute the number of risks in each process and then it will rank. The aim of this study is to obtain maximum likelihood and severity and identify. Then, according to the rankings can mean, median, standard deviation and standard deviation measures for each process to obtain And, finally, his analysis of our study stated.

Results and Discussion

The greatest impact of any process is related to the quality assurance,

The greatest likelihood is related to the quality assurance,

The greatest likelihood of risk associated with the process engineering,

Most of the risk priority number is associated the quality assurance,

Most of the risk priority numbers are in these processes:

The most effective risk known,

109 risks identified, 53 risks were identified, that were evaluated in a

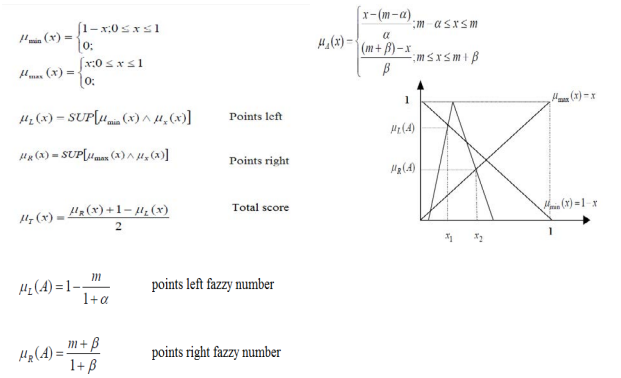

Figure 1: Defuzzicating fuzzy numbers.

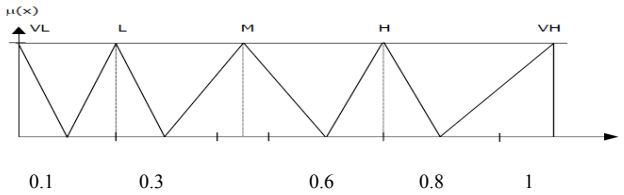

Figure 2: Membership functions of linguistic variables.

Linguistic Variables	Fuzzy value	Points right	Points left	Total score
VL	(0,0.1)	0.91	1	0.046
L	(0.1,0.2,0.3)	0.273	0.82	0.227
M	(0.3,0.4,0.5,0.6)	0.522	0.609	0.457
H	(0.6,0.7,0.8)	0.727	0.364	0.682
VH	(0.8,0.9,1)	1	0.167	0.917

Table 1: The values assigned to each fuzzy numbers.

critical area. And the other one were lower than average risk.

A: Inadequate supervision and lack of verification of quality machinery and equipment IQ-OQ-PQ

B: Production and packaging operator error

From 53 risks, 2 risks were in catastrophic areas and 51 other risks were in critical area (Figure 3). On the other one, we can say: Risk A, B are unacceptable risks and other risks which 51 were undesirable. So, the most effective risks that can affect the quality of the finished product in beta-lactam are 53 risks. The status of QA managers' knowledge is appropriate, but implementation of QA, QC, GMP and manufacturing process in Iranian pharmaceutical industry are not appropriate.

Conclusion

The present study obtained results suggesting that the FMEA method in conjunction with the supporting fuzzy set method can be effectively used for risk assessment in beta-lactam production and pharmaceutical industry as a whole. In this course, the risk assessment is a goal of the research. The risk assessment and quality control system for reliability of beta-lactam productions [10,11].

The considered methods and models can be used to assess risks in

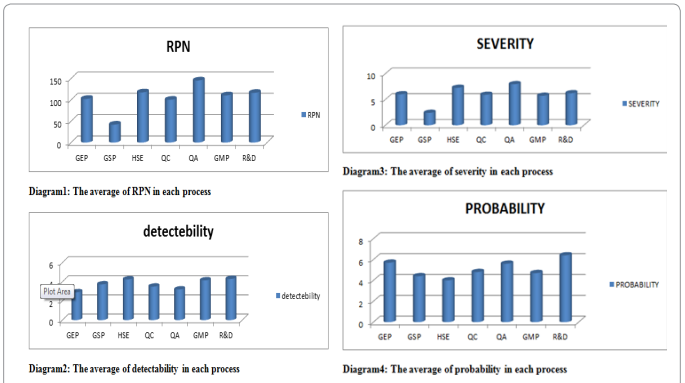

Diagram1: The average of RPN in each process

Diagram3: The average of severity in each process

Diagram2: The average of detectability in each process

Diagram4: The average of probability in each process

Figure 3: Process in the industry.

pharmaceutical company.

In future, we suppose to develop methods for the integration of different information Technologies and methods of analysis (FMEA, fuzzy set theory).

Such techniques can significantly improve the efficiency of solving these risks, which in turn improves the performance indicators and safety of the production as a whole, which is especially important in the current conditions.

The important points are that in comparing the results with previous targets, there are differences.

In many of the risks that were thought to be hazardous to study and was of great importance during the evaluation process, it was least important or very important. It is clear that our view of the study.

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