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An ıntegrated approach by fmea & fuzzy prioritization method at pharmaceutical ındustry quality control

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Abstract

Protecting public health, taking preventive measures and ensuring recovery in case of any disease are conditions for creating a healthy life. In order to create this life, the manufacturing process of the pharmaceutical industry needs to be formed carefully. In this study there is a risk analysis application into operational processes of a pharmaceutical company. In application study, operational processes of sample company were examined and analyzed from October to May. Within the scope of the study, a two-stage approach was proposed in the analysis of the data obtained. In the first phase, fishbone analysis was carried out to determine the risks in the operational processes and the potential risks in two separate production lines were determined. In the second stage, the risk prioritization method was used and risk priority numbers (RPN) were calculated for all risks. In all these analysis, more realistic and valid results were obtained with the usage of fuzzy logic and the calculations of RPNs were made more objective and independent from analysts. After the determination of RPNs, precautions were suggested for high risky failures. Following the implementation of precautions, new RPNs were calculated for all failures. The old and the new RPNs were compared for all risky failures and all precautions were examined with their impacts on the process. As a result, all examined failures' risk prioritization numbers were reduced in the ratio between 72% and 90%, the operational processes were improved.

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1. Introduction

Today companies have to increase their market share and they effort to reduce costs in an increasingly competitive environment. The competition to be continuous, it must be efficient and accurate production. In the factory working conditions, the desired quality and at a certain time to reveal the cost of the desired products are not easy. In this way, firms have to increase their market share and satisfied customers.

Quality can be under defined conditions and within a defined period of time able to carry out the required functions. Quality, along with changing technologies and conditions, it is a constantly evolving concept. This development goes in line with consumer needs. Product must be taken under the quality assurance during the production stages. However, the product quality to measure all properties is not possible in terms of both cost and time. Therefore, various methods are used to determine the important quality characteristics. These methods occur with a low failure rate and low-cost products.

Providing this situation has led to the emergence of the quality control system. Typically, faults in the quality control system, it is trying to catch after the creation of the product. This situation increases costs. In the newly developed quality system, failures are caught before the creation of the design of the product. Thus, the number of defective products and the cost will be reduced.

To ensure that more easily adapt to changing business conditions and critical performance measures used to ensure quality consistency. In this way, the company is evaluated periodically and improvement work is done. With improvements in risk assessment methods, measures are taken to reduce the risk to a minimum. These measures are ranked in order of priority and evaluated. The purpose of the risk assessment is determining the measures to be taken against failures. In this case, failures are determined in advance and occurrence is minimized.

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Failure mode and effects analysis (FMEA) works by analyzing all the failures that may occur during processing and service of a product, these failures are a set of prevention activities. The goal is to eliminate failures that may occur in the production phase determining in advance. As a result of this objective, determining possible failures and their causes, preventive measures are taken. Thus, the customer would have offered zero-defect products.

In literature there are lots of studies about FMEA in different research fields. Especially, in recent years the linguistic variables and fuzzy logic have been applied in FMEA method. For example Carpitella et al. (2018) and Kutlu and Ekmekçioğlu (2012) used fuzzy TOPSIS based fuzzy AHP, Fattahi and Khalilzadeh (2018) applied the extended MULTIMOORA and AHP under fuzzy environment to the risk evaluation, Kumru and Kumru (2013) applied fuzzy FMEA to improve purchasing process in a public hospital, Mandal and Maiti (2014) proposed fuzzy similarity value and possibility theory-based approach for risk analysis, Chen et al. (2014) used a structural model based on the FMEA and fuzzy fault tree for a risk assessment of an oxygen-enhanced combustor, Chanamool and Naenna (2016) applied fuzzy FMEA to improve decision making process in an emergency department in hospitals, Dağsuyu et al. (2016) used classical and fuzzy FMEA in a sterilization unit's risk analysis, Tooranloo and Ayatollah (2016) proposed a model for FMEA based on intuitionistic fuzzy approach and Adar et al. (2017) analyzed risk by FMEA and Fuzzy FMEA of supercritical water gasification system used in the sewage sludge treatment [1-10].

In spite of all these papers there are few papers about FMEA and pharmaceutical industry such as Lv and Liang (2014), Bhattacharya (2015) and Hajimolaali and Asl (2016) [11-13]. These papers are very valuable studies about FMEA and risk management in pharmaceutical industry. On the other hand, Su et al. (2012) adopted FMEA to improve the blood transfusion processes in healthcare sector [14].

On the other hand some researchers studied with extended VIKOR method and FMEA in their papers. For example, Liu et al. (2012) used FMEA with extended VIKOR method under fuzzy environment in risk evaluation, Liu et al. (2015) applied combination weighting and fuzzy VIKOR method to FMEA and Mohsen and Fereshteh (2017) used the extended VIKOR method based on entropy measure for the failure modes risk assessment [15-17].

In literature, there are few papers about our application methods. Such as Mikhailov and Tsvetinov (2004)'s paper is the fundamental of fuzzy prioritization approach, Özfırat (2014)'s paper about a new risk analysis methodology integrating fuzzy prioritization method and FMEA and Rahimi et al. (2016)'s paper about prioritization of failures in radiation therapy delivery [18-20]. Even if both papers used fuzzy prioritization methods for FMEA's first step, they are different from our paper about application field.

After the literature review, it is clear that this paper is the first study about risk assessment analysis with FMEA method and fuzzy prioritization in a pharmaceutical industry. Our case study focuses on our sample company, which is a part of Turkey pharmaceutical sector. We examined our company's risk analysis by FMEA method under fuzzy environment.

This paper is aimed to analyze the risk assessment of failures in our sample company's solid (blister) and liquid (syrup) operation lines. We determined the risks with linguistic variables under fuzzy environment then suggested precautions for minimizing risk levels of high risk failures.

In this study, fuzzy AHP method is used to prioritization the FMEA values with generating pairwise matrixes. Briefly, after all literature review there are two main objectives:

- Proposing a risk assessment method using fuzzy logic in FMEA
- Being the first study in literature, because of using fuzzy prioritization method for risk assessment step of FMEA in a new research area such as pharmaceutical sector.

As an outline, Section 2 includes quality and risk assessment and its methods in pharmaceutical sector. Traditional FMEA method, its purpose, benefits, types and implementation steps are in Section 3. Section 4 explains triangular numbers for fuzzy prioritization method in FMEA. Section 5 includes application part with identifying risks, examining the risks with fuzzy comparison matrixes, weighting importance coefficients, converting them to FMEA degrees, calculating RPN numbers, suggesting precautions and calculating new RPN numbers. Finally, concluding remarks and suggestions for further studies are given in Section 6.

2. Quality and Risk Assessment in Pharmaceutical Sector

Nowadays, with the development of technology and globalization rather a competitive environment is strengthened. There are many tasks to companies in order to survive in this competitive environment. One of them is to uncover a quality product. Quality products to best meet customer requirements. This location should always follow market companies.

The concept of quality has evolved and changed from the old year to the present day. There is no fixed definition. We may face many definitions related to quality. The reason for this is the differences in people's quality perspective. Quality is a proportional relation with customer expectations. If it means a quality brand for a person the other person can mean monetary value. Thus, quality has become a multidimensional concept.

Today, companies are continuing their existence and use of risk assessment techniques to ensure long-term success. Physical, chemical, biological, ergonomic and other hazards are identified dangers that can occur from them. It is considered to be likely to cause risky situations.

2.1. Risk assessment processes in pharmaceutical sector

Today has the largest research and development potential in a global industry because of the risks associated with human life. In line drug policies, both quality and the delivery of medication to the patient in the best economic conditions is the main target. However, in production processes and due to some unusual circumstances that occurred during distribution serious risks can be occurred. Drugs sourced from the treatment of 1.3 million people today suffer and are died 1 person per day. The pharmaceutical industry should be examined carefully serious risk accommodates every stage of production. As a result of a failure to collect any products from the market, it cannot prevent damage caused by people arriving.

2.2. GMP (good manufacturing practices) in pharmaceutical sector

The risk of entanglement of products and services should be preventive measures. For each production stage, different criteria and production location, environment, equipment, special raw materials are available for specific applications. These applications are collected under the name as GMP (Good Manufacturing Practices). GMP is a quality risk approach for applying to minimize risks and if possible for eliminating them. Pharmaceutical production performed by these rules, provided that the healthiest way to reach the patient. Drugs' scientific and technological quality and desired qualifications should be prepared with certain applications. Check the validity of this application and the results are performed for process validation. Validation often used in the pharmaceutical industry, it means to prove the validity of the entire production process. The products produced in standard determined whether control is performed [21].

The purpose of GMP is equipment cleaning and ventilation housekeeping, dual signature use of raw materials by introducing read the barcode, to comply with labeling rules and pay attention to the labeling of raw materials, intermediate labeling of any point in the flow chart, to avoid failures that can occur in the packing section.

In risk assessment, the risks are analyzed and graded to decide whether to tolerate risk, if it cannot tolerate taking necessary precautions to minimize. For risk assessment process firstly the data is collected, the hazards are identified, the sources of hazards are examined and with precautions the hazards are eliminated. In risk assessment methods, assessment varies according to the environment and expectations. In literature there are more than 150 risk assessment methods and standards. FMEA is one of the most popular quality control and risk assessment method.

In FMEA, the product or process is determined before the emergence of failures that can occur and the analysis methods is necessary for measurements.

3. Failure Mode and Effects Analysis (FMEA)

Changing competitive environment within the company's service and in the time until it reaches the customer from the design of their products, they encounter failures. Based on these failures is located in the human factor. These failures make the company become an inefficient and lose customer satisfaction [22].

In other respects, mistakes can hurt financially, spiritually also can lead to serious damage. For example, death is the result of failure, shows the way to the bankruptcy of the company.

When we examine this situation, receiving and resolving action before failures occur, it will increase customer satisfaction. The failure occurred during the production phase will be done at that time will be needed to reduce costs will occur in the future.

Today, customer expectations are constantly evolving. Due to these evolving expectations the companies have not any chance to make a mistake in product or process. So before bringing out a new product, the companies should minimize the risks of mistakes. At this stage, FMEA will help to companies. In the usage of this analysis, the risk of failures will be destroyed and customer expectations will be the best as opposed to.

A correctly applied FMEA, the practitioner system, design, process, and service provides useful information that will allow you to reduce the risks. Therefore, this analysis is a technique for reliability assurance.

FMEA is a powerful risk assessment method. The method examines risks by using qualitative and quantitative data. In short, FMEA technique assess the possible risks that may occur in design, production and services steps of companies and it can help them for reducing or eliminating these risks.

FMEA aims to identify risks in advance is taking precautions. This aim is realized when it increases the competitiveness of companies. Additionally, the minimum risk decreases the cost of failure, providing the quality and reliability of the increase. So, FMEA has been recently used for a preferred method.

The purpose of FMEA is ensuring the resulting product meets the needs of the customer, analyzing the properties of the product of the design phase, finding the causes and effects of the failures, determining the types of failures and taking regulatory measures to eliminate them [23,24].

Successful FMEA will bring positive results. The most important reason for the application of this analysis is to ensure customer satisfaction. The result of the application for the company is quality and development increases.

FMEA, increases customer satisfaction, minimizes costs, improves product's quality and the competitiveness of the company and also increases job security. These benefits are for the customers, employees and companies. On the other hand FMEA has benefits for the process. It reveals failures, ensures timely production, allows recovery of missing the point, prevents the repetition of failures, provides for the reduction of scrap and waste and helps eliminate unnecessary time.

FMEA is applied when a change is to be made in current products, when new products or new process are developed, in the improvement of processes, in ensuring customer satisfaction, safety and job security, improving the system and in cases where existing product and process failures are detected [25].

3.1. Types of FMEA

FMEA can be applied at different stages of the product. The applications are built as hardware for the first time. It is used to determine the failure in the time period. Today it is applied in all kinds of products and services. Depending on the application areas the FMEA types are analyzed in four varieties [22-26-27]:

System FMEA: During the design phase system and sub-systems analysis, FMEA is used for determining the type of failure resulting from system deficiencies. System FMEA aims to provide a balance between the operational factors and economic factors. To achieve this purpose, customer demands and expectations should be considered. The target of this type of FMEA is to improve the quality and reliability of the system.

Design FMEA: Design FMEA is applied before starting production. It examines product failures that will occur because of failures in the design at the manufacturing stage. In short, the determination of all the failures that may arise in the design and properly defined. In design FMEA, there are two opinions. The first one is, generally handled system or product and analyzed down to the smallest part and the second one is started from the smallest parts and advances to the latest state of the system and the product. The selection of opinion depends on the system and the magnitude of the problem.

Process FMEA: Process FMEA is used to examine the manufacturing process. It examines the failure and causes that occur during production. This analysis is used to destroy the types of due to deficiencies in the production and assembly process. All failures do not occur during the production phase, some of them can occur before production. Process FMEA determines the weak points of the production components in the production process such as machine, material, environment and human.

Service FMEA: Service FMEA helps to analyze products before reaching the customer. In service FMEA, workers, environment, methods, procedures should be in interaction with the material factors. These factors result in the formation individually. Service FMEA is a complex technique. In order to understand the root cause of the failure continuous service should be repeated.

3.2. Implementation steps of FMEA

In FMEA, a team is formed where products, production processes or services in the presence of failures, determining the failure risk priorities, the realization of preventive actions for focusing on prevention before reaching the customer. FMEA identifies potential failures and determines the causes and effects of these failures. Necessary observations and studies are done and they can be applied after the proposed reformative actions. The aim is to prevent the products from failures before reaching the customers.

In FMEA implementation firstly the scope of analysis and FMEA team are established. Then the process is examined, failure modes and their causes and impacts are determined. For all failures occurrence, severity and detection values are determined and risk priority number (RPN) is calculated. After suggesting actions and their implementation, new RPN value is calculated [28].

Failure type of internal and external customer needs and does not overlap with the demands and expectations. Failure type of the function of determining, specific criteria such as safety, place, time, method, performance, and cost are taken into consideration due to customer complaint reports, test reports, reliability analysis of the results, related products and system information [29,30].

Determining the failure's criticality levels, occurrence, severity and detection values are calculated. Priority order is determined based on these values. The important thing is to identify mistakes before they happen as early as possible and take measures. Therefore determined value is based on experience and results.

3.2.1. Determination of occurrence values

Occurrence is the possibility of the occurrence of possible causes of failures and causing the type of failure during the use of the product. Shows the occurrence of failures and potential failures of each species is related to the possibility of realization.

Occurrence value of FMEA application is not identified as a possibility. There are two different approaches to determining the value of occurrence, the first approach, a failure type (or reason for failure) to determine the value to occurrence and the second approach is what caused the failure value associated with the occurrence of the type of failure has appeared in its results. The occurrence value of the failure is multiplied by these two probability values. The degree of occurrence to determine is based on Wang et al.'s (2009) paper [31].

3.2.2. Determination of severity values

The potential results of failure, the consequences case of the realization to evaluate the effects on customers. Damage may bring about the risk of severity seen in the past is determined according to similar situations and the people involved experience. The crisp ratings for severity values are based on Wang et al.'s (2009) paper [31].

3.2.3. Determination of detection values

Detection is the degree of failure block access to customers about the availability of existing controls. Possible types of failure, is assumed to occur during the use or the end customer at a later stage, should be passed through the detection measures envisaged. Therefore, the probability values associated with detection, defined as the probability of default, failure to reach customers why they occur.

Detection value is determined by analyzed data from the past and the study benefited from the experience of the team. The Crisp ratings for detection values are based on Wang et al.'s (2009) paper [31].

3.2.4. Calculation of the rpn values

Risk priority number (RPN) is a value obtained by multiplying occurrence, severity and detection values as Eq. (1).

$$\text{Risk Priority Number (RPN)} = \text{Occurrence(O)} \times \text{Severity (S)} \times \text{Detection (D)} \quad (1)$$

RPN is defined and calculated for failures. After this calculation the failures are ranked from small to large due to RPN values. Making reformative actions are started from the largest value after this order. Reformative studies are done on the failure exceeds a

predetermined threshold value for a number of priority risks [15].

In an evaluation of RPN value: if RPN value is less than 40 then there is no need for precaution, if the value is $40 \leq \text{RPN} \leq 100$ precautions can be taken, if RPN value more than 100 the company must take precautions and suggestions for reducing RPN values [32].

After taking precautions, risk priority number is calculated again with new occurrence, severity and detection values. New RPN is expected to be lower than previous calculations. Drop requested is no specific lower limit, which means a reduction in the number of risk priority if success is achieved. If there is no change in the results, studies should be carried out from the beginning, new FMEA studies should be done to reduce the occurrence and severity to determine value.

4. Triangular Numbers for Fuzzy Prioritization Method in FMEA

In this paper, fuzzy numbers are used for prioritization the RPN values as Özfırat (2014)'s study with differences in Analytic Hierarchy Process (AHP) steps [19]. In our proposed model we used Chang's (1996) extent analysis method which is one of the most popular approaches in fuzzy AHP field [33]. The method is used because of its easier calculation steps. Fuzzy AHP is a very useful methodology for important applications in multi-criteria decision making problems under fuzzy environments in recent years [34] and because of human thinking and preferences are inherently imprecise; their vague character can be modelled by fuzzy theory easily [35]. In a method, the decision makers' judgements are treated with pairwise comparisons and the priority vector is found [36,37].
The fuzzy comparison matrixes are used for evaluating the degrees of occurrence, severity and detection with Saaty's scales which is shown in Table 1.

Our proposed method's structure and application steps for prioritizing the risk factors, calculating RPN values under fuzzy environment is given in Fig. 1.

- *Identifying risks and fuzzy comparison matrixes for occurrence, severity and detection:* According to Özfırat (2014)'s study, firstly the risk factors are identified in FMEA and then fuzzy comparison matrixes are generated for occurrence, severity and detection for all risks.
- *Determining importance coefficients (weight vectors) by fuzzy prioritization method:* After generating the fuzzy matrixes, fuzzy prioritization method's step is started. For each comparison matrixes, the weight vectors are calculated with Eq. (2), Eq. (3) and Eq. (4) in this step.

$$W^{OCCURENCE} = (w_1^O, w_2^O, w_3^O, \dots, w_n^O) \quad (2)$$
$$W^{SEVERITY} = (w_1^S, w_2^S, w_3^S, \dots, w_n^S) \quad (3)$$
$$W^{DETECTION} = (w_1^D, w_2^D, w_3^D, \dots, w_n^D) \quad (4)$$

n are the number of risks.

Table 1. Linguistic scale for relative importance [38]

Linguistic scales		Triangular fuzzy numbers	
		Number	Conjugate
Equally important	EI	1, 1, 1	1, 1, 1
Weakly more important	WI	2/3, 1, 3/2	2/3, 1, 3/2
Strongly more important	SI	3/2, 2, 5/2	2/5, 1/2, 2/3
Very strongly more important	VSI	5/2, 3, 7/2	2/7, 1/3, 2/5
Absolutely important	AI	7/2, 4, 9/2	2/9, 1/4, 2/7

- *Converting the importance coefficients (weight vectors) into FMEA degrees:* The importance coefficients are the values of the risks occurrence probability according to each other. These values have to be used and converted FMEA degrees by using Wang et al.'s (2009) paper [31]. For this calculation firstly, the risk which has the highest occurrence value is determined by the experts. This occurrence value can be named as P_1. Then for all risks the occurrence values are calculated as seen in Table 2, D column. Finally, these values are converting to occurrence degrees which are given in Table 2, E column.
  The same calculations are made for severity and detection in Table 3-4.

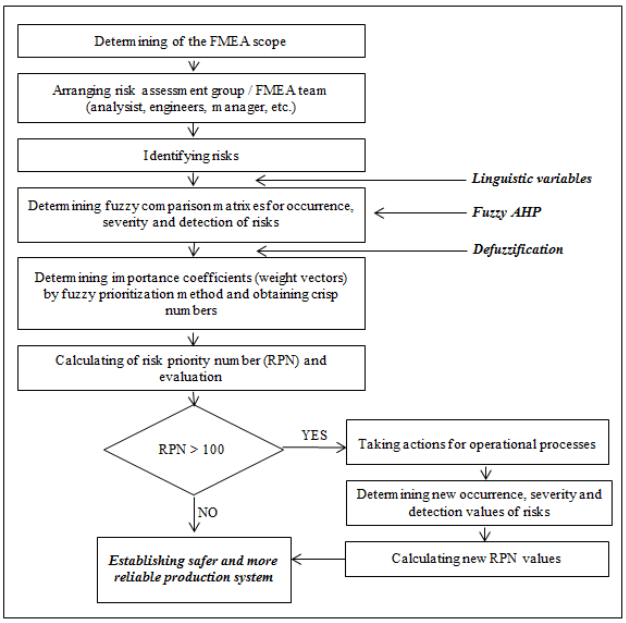

Figure 1. The structure of the proposed method

Table 2. Converting occurrence coefficients found by fuzzy prioritization method into FMEA degrees [19]

A	B	C	D	E
Risks	Weight vector for occurrence	Occurrence (The highest value)	Occurrence by coefficients	Degree (According to Table 1)
R_1	w_1^O	P_1	-	O_1
R_2	w_2^O	-	$P_1 . (w_2^O / w_1^O)$	O_2
...	...	-	...	...
R_n	w_n^O	-	$P_1 . (w_n^O / w_1^O)$	O_n

Table 3. Converting severity coefficients found by fuzzy prioritization method into FMEA degrees [19]

A	B	C	D
Risks	Weight vector for severity	Severity (The highest value, from Table 2)	Degree by according to coefficients
R_1	w_1^S	S_1	S_1
R_2	w_2^S	-	$S_1 . (w_2^S / w_1^S)$
...	...	-	...
R_n	w_n^S	-	$S_1 . (w_n^S / w_1^S)$

Table 4. Converting detection coefficients found by fuzzy prioritization method into FMEA degrees [19]

A	B	C	D
Risks	Weight vector for detection	Detection (The highest value, from Table 3)	Degree by according to coefficients
R_1	w_1^D	D_1	D_1
R_2	w_2^D	-	$D_1 . (w_2^D / w_1^D)$
...	...	-	...
R_n	w_n^D	-	$D_1 . (w_n^D / w_1^D)$

- *Finding RPN values:* For all risks the RPN values are calculated by Eq. (1). If the RPN values are higher than 100, there must be some proactive and reactive precautions and suggestions.

5. Applying Fuzzy FMEA in Operation Processes of A Pharmaceutical Company

The risk assessment is done to review and lists potential failure modes of all blister, bottle, sachet and tube packaging lines used at a sample company which leads to mix-ups and recalls and determines actions for prevention in İstanbul. In the sample company, there are 4 blister lines, 3 bottle lines, 1 tube filling line and 1 sachet filling lines. Our study was performed on the blister and syrup lines. In Fig. 2 there are statistics about headcount of the company and Fig. 3 shows the company's layout plan.

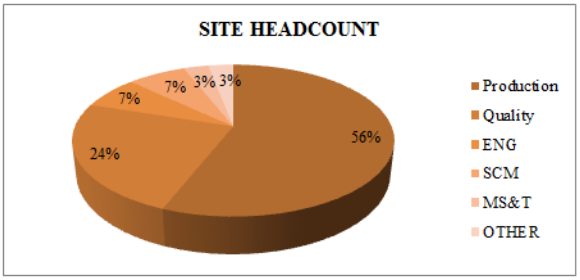

Figure 2. Company statistics

The sample company is a generic pharmaceutical company in all over the world. It has a history of over 120 years and it is a trusted leader who has a reputation for outstanding quality. After the loss of patent protection, quality and affordable medicines development, strategic and customer-oriented approach for manufacturing and marketing has been more important. It now has more than 23,000 employees worldwide in more than 130 countries. It

has a strong presence on all continents today, equivalent in all major markets are represented in a good way and to patients everywhere, doctors, health service providers and job offers remain close partners.

The company has three production plants in Turkey and also it operates with approximately 1,000 employees. Pharmacy Products is a major actor in the generic pharmaceutical market in Turkey. Since 2005, it has exported huge amount of drugs to 46 different countries.

Products are supplied to many countries such as Turkey, Slovenia, Croatia, Singapore, Ukraine, Australia, Brazil, Russia, Chile, Colombia, Thailand, Macedonia, Hong Kong, Taiwan, the Philippines, and Japan.

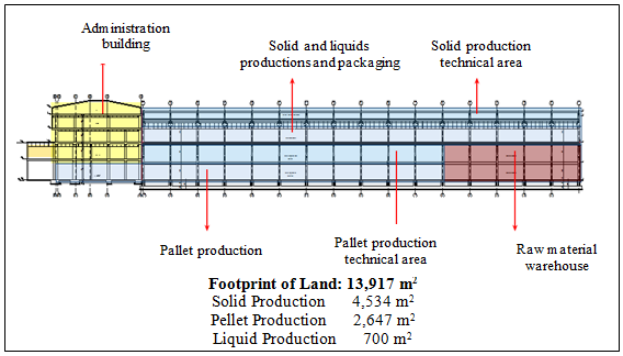

Figure 3. The company plan

5.1. The purpose of application

Human health has great importance in today's growing conditions. Because of this important pharmaceutical companies have a mission for protecting human health. In this case, pharmaceutical companies from product design phase until it reaches the customer in time, cost-effective, should produce fast and faultless. For this purpose, FMEA is a more suitable risk assessment method for examining the common technical failures which are expected and reducing their effects to a minimum.

In company, there are significant risks in the factory, for example mixing in the packaging line may cause many failures. That's why the FMEA application was done in packaging department of company for examining the system and reducing potential risks.

The application is done in solid (blister) and liquid (syrup) packaging lines for preventing occurred operational process failures.

FMEA team is composed of 6 people with different special characteristics and occupational experiences. Team approach has brought together a variety of perspectives and experiences. Fig. 4 shows the FMEA team members.

Name Surname	Position	Function
Analyst 1	Production Team Leader/Packaging Unit	Team Leader
Analyst 2	Liquid & Semi Solid Production Specialist	Team Member
Analyst 3	Product Steward	Team Member
Analyst 4	Product Steward	Team Member
Analyst 5	Industrial Engineer & Intern in the company	Team Member
Analyst 6	Industrial Engineer	Team Member

Figure 4. FMEA team of our study

In this paper, solid and liquid products packaging stage is examined with engineers and assessments have been made on possible failures.

5.2. Identifying risks

During the study, packaging lines are carefully followed and the potential failures are identified. After careful review, there are 19 failures were found in both blistering and syrup filling lines. While the evaluation of failures, previous documents, quality complaints, factory standards and procedures have been reviewed.

First of all, the system works has been analyzed and decided which sections need improving. Material consumption, filling or blistering, carton packing and line release sections are examined.

After review of manufacturing processes and records, potential failures were determined with the responsible people in this section using by brainstorming method. Purpose is determining the root cause of all situations that could create hazards by detecting.

Table 5. Blistering line risks in pharmaceutical company

Failures	Process step	Potential failure	Potential effect	Potential causes
BlisteringF1	Blistering	Leakage in blister	Recall, rework	Equipment, human failure
BlisteringF2	Blistering	Missing tablet in blister	Recall, rework	Equipment
BlisteringF3	Blistering	Mix-up foil of any product	Recall, rework	Human failure
BlisteringF4	Blistering	Pinhole in blister	Recall, rework	Human failure
BlisteringF5	Carton packing	Missing blister and leaflet	Recall, customer complaint, repack	Equipment
BlisteringF6	Carton packing	Damaged on the folding box	Customer complaint	Equipment
BlisteringF7	Carton packing	Wrong label	Customer complaint	Human failure
BlisteringF8	Material Consumption	Unprinted packaging material	Packaging material mix-up, reject	Supplier failure
BlisteringF9	Material Consumption	Contaminated packaging material	Recall, customer complaint	Human failure

Failures syrup and tablets (blistering) were examined for over two lines. The failures can be seen at which process step, its effects and causes are listed as in Table 5 and Table 6 and also Fig. 5 shows fishbone analysis of blistering line failures and Fig. 6 shows fishbone analysis of syrup filling line failures.

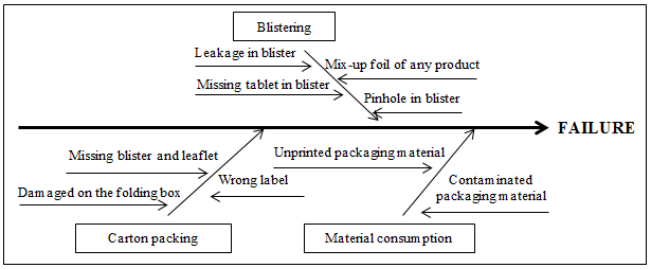

Figure 5. Fishbone analysis of blistering line failures

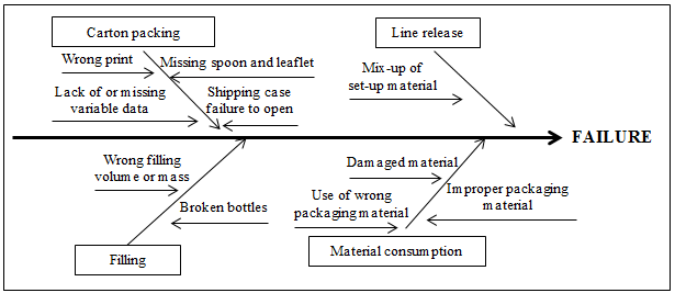

Figure 6. Fishbone analysis of syrup filling line failures

Table 6. Syrup filling line risks in pharmaceutical company

Failures	Process step	Potential failure	Potential causes	Potential effects
SyrupF1	Filling	Broken bottles	Machine failure, supplier failure	Reject, customer complaint
SyrupF2	Filling	Wrong filling volume or mass	Equipment setting, human failure	Recall, customer complaint, reject
SyrupF3	Carton packing	Wrong print	Human failure	Recall, customer complaint
SyrupF4	Carton packing	Lack of or missing variable data	Equipment, failure in embossing	Recall, repack
SyrupF5	Carton packing	Missing spoon and leaflet	Equipment, failure in sensor	Recall, customer complaint
SyrupF6	Carton packing	Shipping case failure to open	Supplier failure	Machines stop
SyrupF7	Material consumption	Damaged material	Human failure in transportation, supplier failure	Customer complaint
SyrupF8	Material consumption	Improper packaging material	Human failure	Recall, customer complaint, reject
SyrupF9	Material consumption	Use of wrong packaging material	Human failure	Packaging material mix-up, reject
SyrupF10	Line release	Mix-up of set-up material	Human failure	Customer complaint

5.3. Developing fuzzy pairwise comparison matrixes

In fuzzy prioritization method the AHP method is performed firstly. In fuzzy AHP, the questionnaire can be performed for the comparison of the importance or preference of risk according to others for understanding the importance degree of the risks for each other. Table 7-12 show fuzzy assessment matrixes for occurrence, severity and detection of the risks respectively for two packaging lines (blistering and syrup filling).

Table 7. Fuzzy pairwise comparison matrix for occurrence of risks in blistering line

	BF_1	BF_2	BF_3	BF_4	BF_5	BF_6	BF_7	BF_8	BF_9
BF_1	EI		SI	SI				SI	SI
BF_2	VSI	EI	AI	AI	SI	SI	WI	AI	AI
BF_3			EI	WI				WI	WI
BF_4			WI	EI				WI	WI
BF_5	SI		VSI	VSI	EI	WI		VSI	VSI
BF_6	SI		VSI	VSI	WI	EI		VSI	VSI
BF_7	VSI	WI	AI	AI	SI	SI	EI	AI	AI
BF_8			WI	WI				EI	WI
BF_9	WI		WI	WI				WI	EI

$W_{OCCURENCE-BFR} = (0.08, 0.21, 0.07, 0.07, 0.11, 0.11, 0.21, 0.07, 0.07)^T$

Table 8. Fuzzy pairwise comparison matrix for severity of risks in blistering line

	BF_1	BF_2	BF_3	BF_4	BF_5	BF_6	BF_7	BF_8	BF_9
BF_1	EI	WI	WI	SI	SI	AI	AI	SI	VSI
BF_2	WI	EI	WI	SI	SI	AI	AI	SI	VSI
BF_3	WI	WI	EI	SI	SI	AI	AI	SI	VSI
BF_4				EI	WI	VSI	VSI	WI	SI
BF_5				WI	EI	VSI	VSI	WI	SI
BF_6						EI	WI		
BF_7						WI	EI		
BF_8				WI	WI	VSI	VSI	EI	SI
BF_9						SI	SI		EI

$W_{SEVERITY-BFR} = (0.19, 0.19, 0.19, 0.08, 0.08, 0.06\ 0.06, 0.08, 0.07)^T$

Table 9. Fuzzy pairwise comparison matrix for detection of risks in blistering line

	BF_1	BF_2	BF_3	BF_4	BF_5	BF_6	BF_7	BF_8	BF_9
BF_1	EI	VSI	AI	AI	WI	SI	AI	SI	SI
BF_2		EI	SI	SI			SI		
BF_3			EI	WI			WI		
BF_4			WI	EI			WI		
BF_5	WI	VSI	AI	AI	EI	SI	AI	SI	SI
BF_6		SI	VSI	VSI		EI	VSI	WI	WI
BF_7			WI	WI			EI		
BF_8		SI	VSI	VSI		WI	VSI	EI	WI
BF_9		SI	VSI	VSI		WI	VSI	WI	EI

$W_{DETECTION-BFR} = (0.20, 0.09, 0.07, 0.07, 0.20, 0.10, 0.07, 0.10, 0.10)^T$

Table 10. Fuzzy pairwise comparison matrix for occurrence of risks in syrup filling line

	SF_1	SF_2	SF_3	SF_4	SF_5	SF_6	SF_7	SF_8	SF_9	SF_{10}
SF_1	EI	SI		SI	VSI	SI		VSI	SI	SI
SF_2		EI		WI	SI	WI		SI	WI	WI
SF_3	SI	VSI	EI	VSI	AI	VSI	WI	AI	VSI	VSI
SF_4		WI		EI	SI	WI		SI	WI	WI
SF_5					EI			WI		
SF_6		WI		WI	SI	EI		SI	WI	WI
SF_7	SI	VSI	WI	VSI	AI	VSI	EI	AI	VSI	VSI
SF_8					W			EI		
SF_9		WI		WI	SI	WI		SI	EI	WI
SF_{10}		WI		WI	SI	WI		SI	WI	EI

$W_{OCCURENCE-SFR} = (0.10, 0.08, 0.19, 0.08, 0.06, 0.08, 0.19, 0.06, 0.08, 0.08)^T$

Table 11. Fuzzy pairwise comparison matrix for severity of risks in syrup filling line

	SF_1	SF_2	SF_3	SF_4	SF_5	SF_6	SF_7	SF_8	SF_9	SF_{10}
SF_1	EI	VSI	AI	SI	SI	AI	SI	WI	WI	SI
SF_2		EI	SI			SI				
SF_3			EI			WI				
SF_4		SI	VSI	EI	WI	VSI	WI			WI
SF_5		SI	VSI	WI	EI	VSI	WI			WI
SF_6			WI			EI				
SF_7		SI	VSI	WI	WI	VSI	EI			WI
SF_8	WI	VSI	AI	SI	SI	AI	SI	EI	WI	SI
SF_9	WI	VSI	AI	SI	SI	AI	SI	WI	EI	SI
SF_{10}		SI	VSI	WI	WI	VSI	WI			EI

$W_{SEVERITY-SFR} = (0.17, 0.07, 0.05, 0.08, 0.08, 0.05, 0.08, 0.17, 0.17, 0.08)^T$

Table 12. Fuzzy pairwise comparison matrix for detection of risks in syrup filling line

	SF_1	SF_2	SF_3	SF_4	SF_5	SF_6	SF_7	SF_8	SF_9	SF_{10}
SF_1	EI	WI	SI	SI	SI	SI			SI	WI
SF_2	WI	EI	SI	SI	SI	SI			SI	WI
SF_3			EI	WI	WI	WI			WI	
SF_4			WI	EI	WI	WI			WI	
SF_5			WI	WI	EI	WI			WI	
SF_6			WI	WI	WI	EI			WI	
SF_7	SI	SI	VSI	VSI	VSI	VSI	EI		VSI	SI
SF_8	VSI	VSI	AI	AI	AI	AI	SI	EI	AI	VSI
SF_9			WI	WI	WI	WI			EI	
SF_{10}	WI	WI	SI	SI	SI	SI			SI	EI

$W_{DETECTION-SFR} = (0.11, 0.10, 0.07, 0.07, 0.07, 0.07, 0.12, 0.21, 0.07, 0.11)^T$

5.4. Computing importance coefficients with fuzzy prioritization method

After operating fuzzy AHP steps we calculated weight vectors for three dimensions such as occurrence, severity and detection. The calculated importance coefficients in other words weight vectors are shown in Table 13 and Table 14 for three FMEA indicators.

Table 13. Importance coefficients computed by fuzzy prioritization method

	Occurrence / W_{O-BFR}	Severity / W_{S-BFR}	Detection / W_{D-BFR}
BF_1	0.08	0.19	0.20
BF_2	0.21	0.19	0.09
BF_3	0.07	0.19	0.07
BF_4	0.07	0.08	0.07
BF_5	0.11	0.08	0.20
BF_6	0.11	0.06	0.10
BF_7	0.21	0.06	0.07
BF_8	0.07	0.08	0.10
BF_9	0.07	0.07	0.10

Table 14. Importance coefficients computed by fuzzy prioritization method

	Occurrence / W_{O-SFR}	Severity / W_{S-SFR}	Detection / W_{D-SFR}
SF_1	0.10	0.17	0.11
SF_2	0.08	0.07	0.10
SF_3	0.19	0.05	0.07
SF_4	0.08	0.08	0.07
SF_5	0.06	0.08	0.07
SF_6	0.08	0.05	0.07
SF_7	0.19	0.08	0.12
SF_8	0.06	0.17	0.21
SF_9	0.08	0.17	0.07
SF_{10}	0.08	0.08	0.11

5.5. Converting importance coefficients into fmea degrees and calculating rpn values

The importance coefficients which are given in Table 17-18 are converted FMEA degrees. In these conversions Table 5 is used for occurrence, Table 6 is used for severity and Table 7 is used for detection, respectively.

After calculating the degrees of occurrence, severity and detection, the RPN values are computed according to Eq. (1). The calculated FMEA degrees and RPN values are shown in Table 15 and Table 16. Some RPN values shown in these tables are higher than 100. That's mean we have to suggest proactive and reactive precautions for these risks.

After calculating the number of risk priorities, the failures' percentages weights and cumulative percentages weights were calculated and failures were ordered from bigger to smaller in Table 17 and Table 18.

The possible failures in blistering and syrup filling line are examined and RPN values are formed with Pareto analysis. Identified potential failures and considering of these causes and effects, RPN values are calculated. Pareto analysis is used to separate major and minor causes of the problem from each other with 80-20 rule. This technique helps to identify the top 20% of causes that needs to be addressed to resolve the 80% of the problems. Pareto analysis was determined by high-risk failures. Pareto diagram drawn by 80% limit of the value of the RPN forming failures identified and it proposed reformative actions for these failures. Leakage in blister and improper packaging material are important problems according to Pareto analysis.

Table 15. Computing occurrence, severity, detection degrees and RPN for blistering line

Risks	Occurrence coefficient	Occurrence according to coefficient	Occurrence degree (O)	Severity coefficient	Severity degree (S)	Detection coefficient	Detection degree (D)	RPN
BF_1	0.08	0.000066	2	0.19	9	0.20	9	**162**
BF_2	0.21	0.000173	3	0.19	9	0.09	4	**108**
BF_3	0.07	0.000058	2	0.19	9	0.07	3	54
BF_4	0.07	0.000058	2	0.08	4	0.07	3	24
BF_5	0.11	0.000091	3	0.08	4	0.20	9	**108**
BF_6	0.11	0.000091	3	0.06	3	0.10	5	45
BF_7	0.21	0.000173	3	0.06	3	0.07	3	27
BF_8	0.07	0.000058	2	0.08	4	0.10	5	40
BF_9	0.07	0.000058	2	0.07	3	0.10	5	30

Table 16. Computing occurrence, severity, detection degrees and RPN for syrup filling line

Risks	Occurrence coefficient	Occurrence according to coefficient	Occurrence degree (O)	Severity coefficient	Severity degree (S)	Detection coefficient	Detection degree (D)	RPN
SF_1	0.10	0.0450	6	0.17	10	0.11	3	**180**
SF_2	0.08	0.0020	4	0.07	4	0.10	3	48
SF_3	0.19	0.0520	7	0.05	3	0.07	2	42
SF_4	0.08	0.0020	4	0.08	5	0.07	2	40
SF_5	0.06	0.0012	4	0.08	5	0.07	2	40
SF_6	0.08	0.0020	4	0.05	3	0.07	2	24
SF_7	0.19	0.0520	7	0.08	5	0.12	3	**105**
SF_8	0.06	0.0012	4	0.17	10	0.21	6	**240**
SF_9	0.08	0.0020	4	0.17	10	0.07	2	80
SF_{10}	0.08	0.0020	4	0.08	5	0.11	3	60

Table 17. The percentages of risks in blistering line

	Potential Failures	RPN	Percentages (%)	Cumulative Percentage
BF_1	Leakage in blister	162	27.0	27.0
BF_2	Missing tablet in blister	108	18.0	45.0
BF_5	Missing blister and leaflet	108	18.0	63.0
BF_3	Mix-up foil of any product	54	9.0	72.0
BF_6	Damaged on the folding box	45	7.5	79.5
BF_8	Unprinted packaging material	40	7.0	86.5
BF_9	Contaminated packaging material	30	5.0	91.5
BF_7	Wrong label	27	4.5	96.0
BF_4	Pinhole in blister	24	4.0	100.0
	TOTAL	598		

Table 18. The percentages of risks in syrup filling line

	Potential Failures	RPN	Percentages (%)	Cumulative Percentage
SF_8	Improper packaging material	240	27.9	27.9
SF_1	Broken bottles	180	21.0	48.9
SF_7	Damaged material	105	12.2	61.1
SF_9	Use of wrong packaging material	80	9.3	70.4
SF_{10}	Mix-up of set-up material	60	7.0	77.4
SF_2	Wrong filling volume or mass	48	5.6	83.0
SF_3	Wrong print	42	4.9	87.9
SF_4	Lack of or missing variable data	40	4.7	92.6
SF_5	Missing spoon and leaflet	40	4.7	97.3
SF_6	Shipping case failure to open	24	2.7	100.0
	TOTAL	859		

5.6. Precautions for operational processes of a pharmaceutical company and new rpn

As seen in Fig. 6 and Fig. 7, six of 19 failures' RPN values are higher than 100. That's mean we have to suggest precautions and try to decrease occurrence, severity and detection degrees of these failures.

	Potential Failures	RPN	Process step
BF_1	Leakage in blister	162	Blistering
BF_2	Missing tablet in blister	108	Blistering
BF_5	Missing blister and leaflet	108	Carton packing
BF_3	Mix-up foil of any product	54	Blistering
BF_6	Damaged on the folding box	45	Carton packing
BF_8	Unprinted packaging material	40	Material consumption
BF_9	Contaminated packaging material	30	Material consumption
BF_7	Wrong label	27	Carton packing
BF_4	Pinhole in blister	24	Blistering
	TOTAL	598	

Figure 6. The risk priority number evaluation in blistering line

	Potential Failures	RPN	Process step
SF_8	Improper packaging material	240	Material consumption
SF_1	Broken bottles	180	Filling
SF_7	Damaged material	105	Material consumption
SF_9	Use of wrong packaging material	80	Material consumption
SF_{10}	Mix-up of set-up material	60	Line release
SF_2	Wrong filling volume or mass	48	Filling
SF_3	Wrong print	42	Carton packing
SF_4	Lack of or missing variable data	40	Carton packing
SF_5	Missing spoon and leaflet	40	Carton packing
SF_6	Shipping case failure to open	24	Carton packing
	TOTAL	859	

Figure 7. The risk priority number evaluation in syrup filling line

In Fig. 8 and Fig. 9 show precautions and after implementation of these precautions re-determined severity, occurrence, detection values and new RPN for risky 6 failures in blistering and syrup filling lines, respectively.

System : Blistering line
Subsystem : Material consumption, line release, blistering, cartooning
Component : Solid

Potential Failure Mode and Effects Analysis (Design FMEA)

FMEA number : 1
Prepared by : Nilay, Seren, İrem
FMEA date : 14.01.2016
Revision date : 26.06.216

Item / Function	Potential Failure(s)	Potential Effect(s)	Potential Cause(s) / Mechanism(s)	RPN	Action taken	S_{new}	O_{new}	D_{new}	RPN_{new}
Blistering	Leakage in blister	Recall, rework	Equipment, human error	162	When the temperature value is incorrect, the blister does not stick. Therefore, the temperature setting should be checked frequently. Cleaning controls should be increased and final control should be checked by engineers.	6	1	6	36
Blistering	Missing tablet in blister	Recall, customer complaints, repack	Equipment setting, human error	108	Checking weigher should be done 2 times or sensitivity should be increased. Appearance testing should be done on samples.	5	2	3	30
Carton packing	Missing blister and leaflet	Recall, customer complaints, rework	Equipment, human error	108	Before entering the folding box the blister should be inspected visually. New line arrangement can be made.	4	2	2	16

Figure 8. Precautions are taken for three failures in blistering line

System : Syrup filling line
Subsystem : Material consumption, line release, blistering, carton packing
Component : Liquid

Potential Failure Mode and Effects Analysis (Design FMEA)

FMEA number : 2
Prepared by : Nilay, Seren, İrem
FMEA date : 14.01.2016
Revision date : 26.06.216

Item / Function	Potential Failure(s)	Potential Effect(s)	Potential Cause(s) / Mechanism(s)	RPN	Action taken	S_{new}	O_{new}	D_{new}	RPN_{new}
Material consumption	Improper packaging material	Recall, customer complaints, reject	Human error	240	Take action urgently. The company should arrange technical visits to suppliers in regular intervals and line control can be done.	4	3	5	60
Filling	Broken bottles	Reject, customer complaints	Machine failure, supplier error	180	Operators should read the barcodes before bringing on line the packaging material and also operators should be trained about the quality of the system. The effectiveness of this training should be tested.	6	1	3	18
Material consumption	Damaged material	Customer complaints	Supplier, human error in transportation	105	The failure is originated from the machine, line arrangements can be made. The supplier of sourced warehouse checks should be increased.	4	2	2	16

Figure 9. Precautions are taken for three failures in syrup filling line.

Table 19. Old and new RPN values for risky six failures

	Potential Failures	RPN	New RPN	Changes (%)
SF_8	Improper packaging material	240	60	75.0
SF_1	Broken bottles	180	18	90.0
BF_1	Leakage in blister	162	36	77.8
BF_2	Missing tablet in blister	108	30	72.2
BF_5	Missing blister and leaflet	108	16	85.2
SF_7	Damaged material	105	16	84.8

In this paper, we analyzed our sample pharmaceutical company's risk assessment with fuzzy FMEA technique. In this application failures were identified and listed, their occurrence, severity and detection degrees were calculated by fuzzy prioritization method. Then the precautions were suggested for risky six failures. After implementation of these precautions the new occurrence, severity and detection degrees were calculated by classical FMEA technique. In Table 19, new RPN values and the changes between old and new RPN's are seen. Also, Fig. 10 shows the comparison of old and new RPN values histogram.

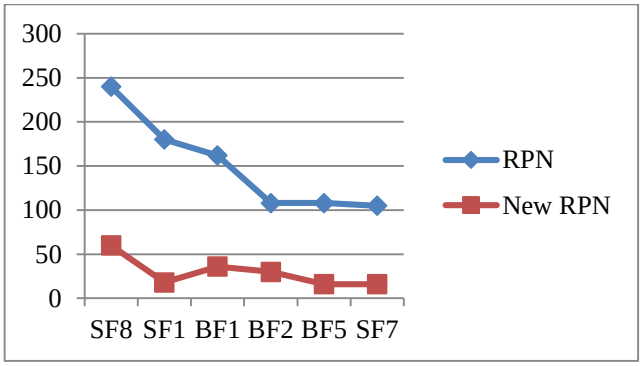

Figure 10. The comparison histogram of old and new RPN values

After our precautions are taken, we decreased our 6 RPN values of the failures. Improper packaging material failure's RPN value was changed from 240 to 60, broken bottles failure's RPN value was changed from 180 to 18, leakage in blister failure's RPN value was changed from 162 to 36, missing tablet in blister failure's RPN value was changed from 108 to 30, missing blister and leaflet failure's RPN value was changed from 108 to 16 and damaged material failure's RPN value was changed from 105 to 16.

In this way, our 6 failures RPN values are lower than 100 and now the values are $40 \leq RPN \leq 100$ extra precautions can be taken in the next days.

4. Conclusions

In today's advancing technology, risks have to be identified in the design phase of the product for minimizing potential failures. Due to providing quality products for customers protects the companies' high position in the market.

In this paper, we applied FMEA technique with fuzzy prioritization method for a pharmaceutical company. Failures and risks were determined which were seen in blister and syrup filling lines by brainstorming and fishbone analysis in FMEA team. Each line was examined separately. For all potential risks severity, detection and occurrence values were determined. These values were obtained by comparison matrixes with triangular numbers under fuzzy environment. By multiplying FMEA indicators, the risk priority number value was calculated. By using the Pareto analysis, these values were ranked in order of importance and percentage values were found. Pareto analysis was performed separately for blister and syrup filling line. After this analysis some precautions were suggested for 6 risky failures and tried to reduce RPN values of them.

As a result, all risky failures RPN values were reduced in the ratio between 72% and 90%. This efficiency can be realized by investments to be made on the equipment, employees and supplier.

This paper is the first study due to its solution techniques in sectoral manner such as FMEA with fuzzy prioritization method. Our research paper, will shed light for different implementation of the risk assessment problems in other sectoral fields with similar techniques in future researches.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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