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A Review of Drugs Supply Disruption Risks and Effects that Lead to Shortage

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The objective of this paper is to give an estimation of drugs supply disruptive risks, which lead to a shortage. The literature analysis showed 15 drivers of supply disruptions and also, three main categories of risks (delays, forecasts and inventory), which produce a negative effect from what was intended; the return to low utilisation of supply service. These disruptions mean that if all required is not in place, shortage appears. There is a lack of knowledge of effects examination because not that many studies have been carried out from the perspective of drugs shortage. The study consists of two parts. The first part is dedicated to methods applicable for risks analysis, whereas the second one is dedicated to practical risks assessment and shortage analysis. The scope of disruption risks is limited in the paper and includes non-systematic risks (i.e., micro risks). Based on approximation data, the author has constructed a methodology for the identification of products, which face a higher risk to have shortage and a probability of getting it. The case analysis of Lithuania for drug shortage in the period 2018 is presented.

Keywords: *Disruption, Drug shortage, Metrics, Supply*.

Introduction

In a functioning health system, equitable access to essential drugs and medicines should be ensured. If this condition is not followed, shortage appears. AHPSR's (The Alliance for Health Policy and Systems Research) observation states that systemic disruptions and their impacts have hardly been studied. The main supply disruptions are identified and presented as follows:

1) The lack of information among distribution chain partners.
2) The unavailability of drugs and delays in the distribution channel.
3) The multiplicity of distribution channel parties and the difficulty of identifying responsible one or negative attitude of providers.
4) Deficiencies in planning and communication.
5) Under-distributing system improvement, difficulties in meeting expenses, and frozen working capital and operational costs for over-distribution in the chain.

The author has identified the main risks under delays, forecast and inventory categories, and has also specified methods applicable for risks analysis. A methodology has been suggested, which aims to categorize products based on the probability of risk occurrence and, to identify the result after a disruption.

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Literature Review

There are many risks in the supply chain when unexpected events happen and the smooth flow of drugs from producers to patients might be disrupted. The topic of risk assessment is widely discussed in various study fields, such as economics and strategic and international management (Alruthia et al. 2018, Tang and Musa 2011).

Lavastre et al. (2012) emphasised three elements to define a risk: the occurrence of lost (number of lost events), its importance (size of lost) and its probability of appearance (uncertainty of lost events). The probability of loss and the significance of it, could be researched from two different perspectives, from enterprise position and from a patient position.

Literature separates macro risks and micro risks. Some examples of macro risks are mentioned. Klibi et al. (2010) analysed disruption sources and discussed environmental events. Blome and Schoenherr (2011) pointed out that the supply chain became more complex and such resulted in higher supply system vulnerability. Juttner (2005) highlighted security and Wakolbinger and Cruz (2011) promoted risk-sharing contracts. They state that in recent years the macro disruptions have been caused by fuel protests, by terrorist attacks, which widely affected system vulnerability. Tang (2006) stated that due to uncertainties in producing unique flu vaccine formula, also unstable market demand, and price pressure from the USA government caused shortages, as many flu vaccine producers left the market. The reducing number of flu vaccine producers left Americans at risk (Tang 2006). Hendricks and Singhal (2005) explained that focus on efficiency in recent years (i.e., lowering costs) caused the increase of supply disruptions, for which management companies did not place enough the effort.

The author has analysed research papers and provided three main categories of risks, which all are shown in Table 1.

According to Tang and Tomlin (2016), risks measurement has two dimensions, the probability of occurrence and the effect of fault. Baghalian et al. (2013) separated risks into two categories, systematic risks related to environmental factors, not controlled by companies, and non-systematic risks, related to factors controlled by the enterprise, i.e., internal facility disruptions. Sadghiani et al. (2015) noticed that the mitigation of non-systematic risks could increase competitive advantage. Simchi-Levi et al. (2014) highlighted frequent non-systematic disruptions: unreliable supplier, inaccurate forecast, unreliable transport system, and stated that historical data could help to quantify the level of risk. Scholten et al. (2014) explained that building the resilient supply chain could lead to avoiding exposure (vulnerability) of risks. Juttner et al. (2003) presented the broader picture and stressed the lack of ownership for highly integrated systems, where companies face the risks of product obsolescence, the lack of responsiveness and this causes shortages.

Table 1. *List of Micro Risks and Research Interest*

Main Risks	Drivers of Micro Risks	Authors
Delays	Accidents	Christopher and Peck 2004
	Equipment and labour issues	Kleindorfer and Saad 2005
	Operational performance	Hendricks and Singhal 2005, Lio and Liu 2019
	Unreliable transport system	Christopher and Peck 2004
	Packing material	Atilgan and McCullen 2007
	Unreliable supplier	Chopra et al. 2007
Forecast	Lack of visibility in the supply chain	Heckmann et al. 2015
	Inaccurate forecast	Chopra and Sodhi 2014
	Under-estimated demand due to shortage cases	Tummala and Schoenherr 2011
Inventory	Product obsolescence	Tummala and Schoenherr 2011
	Damages during the supply process	Sawik 2013
	Human error	Atilgan and McCullen 2007
	Mismatch of physical and system stock	Atilgan and McCullen 2007
	Quality problems	Christopher and Peck 2004, Sawik 2013
	Coordination	Wagner and Bode 2008, Schmitt and Singh 2009, Zhao and Zhu 2018

Methods Applicable for Risks Analysis

In the supply process, a supplier (or resource) is upstream or downstream. When a supplier is upstream, it supplies quantity in full and on time, but downstream the order could not be supplied. Bode and Wagner (2015) use standard accident theory to explain downstream supply chain disruptions. In the literature, the supply-disruption process is analysed from a single supplier side perspective.

Two different categories of models are provided by the authors, yield-uncertainty models and supply-disruption models. The first type of models differs from the second type of models. There is no supply uncertainty in yield-uncertainty models. Most of the models focus on single-period cases, and only a few of them are dedicated to multi-period. The ability of a company to adjust capacity is the multi-period setting. The central aspect of yield-uncertainty models is that company chooses inventory quantity, and this decision directly influences capability during a contingency case. Enterprises managing risks, usually overlook this aspect over products supply chains.

Another type of models is supply-disruption models. Supply-disruption models differ from demand-uncertainty models. In contrast, yield-uncertainty

refers to a single form of supply uncertainty in cases when the quantity produced or inbounded is different from the quantity ordered. Papers presenting optimal strategy are dealing with supply disruption, which is opposite to demand uncertainty, dealing with random quantity and happening more frequently (for every order) but less severe than supply uncertainty (Snyder and Shen 2006). In most of the models, supply disruption means the inability to provide any products (Snyder et al. 2016). Snyder et al. (2006) delivered a model which focuses on order supply-disruptions in the downstream supply chain. Serel (2008) presented a model for upstream supply chain, which is a single period with one supplier facing supply disruption. Tomlin (2006) delivered a study, focusing on the optimal ordering policy. Furthermore, Hou et al. (2010) presented the optimal ordering policy under intermittent supply disruption.

There are three models with supply uncertainty with different probability and various periods versions single, or multiple. All models prove optimal ordering policy. The first model assumes the probability that a supplier delivers an order. This probability is random. The second and third models consider yield uncertainty, where demand itself is stochastic but has continuous distribution. There are also models, which cover both demand (DU) and supply (SU) uncertainties. In those models one SU or DU respectively is deterministic, for example, when supply is uncertain, demand is deterministic, and vice-versa. The result of these models is the highlight of different strategies that are appropriated. To compare demand uncertainty and supply uncertainty authors define the level of uncertainty in the percentage of appeared uncertainty cases. For risk analysis, three primary methods are used:

1. Probability analysis.
2. Shortage causes tree analysis and causal modelling.
3. System vulnerability analysis.

Below is a description of these methods:

1. Probability analysis - processes may have the same probability of being disrupted, but the disruption length could be different. Under different probability and severity are modelled scenarios of disruptions (Deleris and Erhun 2005). Some studies try to determine the probability of lost sales volume but not the size of lost sales; the model scenarios of multi-product or multiple supply sources. Other authors just delivered case analysis. For example, Jaberidoost et al. (2015) have used probability analysis to analyse regulatory risks in Iran. The above-mentioned authors classified risks into financial management risks, sales management, operation management, quality management and supply & suppliers issues and others. For each type of risk, they estimated the probability to identify top risks. Afterwards, they constrained probability-hazard chart. The probability component is also included in economic models. One of such models is Shavell model, where probability is treated as a disruption during a time frame, as a function of investments to mitigate the probability of disruption or resulting

losses. The Shavell model is the most straightforward useful framework in the area of risk analysis, leading to more effective risk mitigation expenditures and reduced accident rates (Kleindorfer and Saad 2005).

2. Shortage causes tree analysis (FTA) and causal modelling - it is partly covered by the ISO 31000 Risk Management Standard (Bharathy and McShane 2014).

The first technique is the fault-tree analysis (FTA). The fault-tree is a graphical representation that shows how shortage event could occur in various ways by systematical identification of the probable sequence of events.

In the literature, a lot of quantitative models are delivered (Ho et al. 2015). Tang (2006) revised around 200 articles, which rely on quantitative models. Halpern and Pearl offered the precise modelling of many meaningful causal relationships (Eiter and Lukasiewicz 2012). Eiter and Lukasiewicz (2012) have delivered causal models with week and actual causes and offered the reduction of weak causes. More than 50 internal and environmental characteristics are used for these analyses and prove cause-and-effect hypothesis raised by authors. By using descriptive statistics, analysis is presented, and regression results are reported, often for many potential predictor variables.

There is also a linear regression analysis for these types of cases. In these models, regression results are often transmuted directly into causal claims (e.g., identified risk characteristics leading to such consequences) or causal implications (e.g., focusing on the changes of identified risk characteristics aiming to improve overall outcome). At the end of the synthesis application, the result of formed linear regression models with limited evidence of causal relationship is provided. Statistical tests of variables and interactions are not adjusted for more proximate characteristics, such as communication, which are added in higher-level models. A hypothesis is usually supported by the statistical significance of the interaction among partners in the supply chain.

Causal effects in regression models also can be analysed from the hierarchical (or sequential) approach. The hierarchical (or sequential) approach involves comparisons across a series of theory-informed regression models in which independent variables are sequentially added in small subsets. The ordering of these models is critical, as all variables are statistically adjusted for all other variables in the same model and previous models, but not for variables in subsequent models. One critical hypothesis tested in the model, was the interaction between inventory level and drug shortage (Chabner 2011, De Weerdt et al. 2015, Ridley et al. 2016).

Another option is to apply the elaboration method, developed in the 1940s, for causal modelling. This method begins with the specification of a hypothesised causal relationship between a pair of variables (referred to as the focal relationship) and employs a series of regression models to rule out alternative explanations. One such analysis provided evidence in support of the hypothesised mediating role of forecasting on the focal relationship between supply chain parties.

One more complex option includes path analysis, structural equation modelling, and graphical models. These assume causal links and the strength of the links for the correct representation of reality. All these sophisticated tools are used to support the development and comparison of explanatory regression models under the guidance of an explicit theoretical framework. They can provide useful directions or standardised approaches, but they do not represent the process of causality research. Researchers make a comparison of regression models and evaluation of theory-driven hypotheses in many ways, and provide compelling arguments involving carefully developed evidence and propose solutions for implications, which bring outcome if theory-based regression analysis is applied correctly.

Two-stage least square (TSLS) is widely used in econometrics to estimate parameters in systems of linear equations. One of the known models is called the Rubin causal model, developed in 1974. TSLS could be used to estimate the average causal effect of a variable, such as a drug dosage. The average causal effect is different from the absence of treatment. It is built by giving the assumptions for probability together with the interval required to respond to appropriately defined causality (Angrist and Imbens 1995).

Sensitivity analysis is an essential tool for the evaluation of mathematical models (Enyinda et al. 2010). In practice, the sensitivity analysis is carried out by changing the parameters and getting an overview of the most sensitive components of the model. The sensitivity analysis is carried out at two or more levels of parameter changes. Sensitivity analysis can be used for the identification of model uncertainties and for determining potential areas for further analysis (Lehr et al. 1994).

3. For system vulnerability analysis, multiple criteria evaluation methods are used. Different types of methodologies have been proposed for system vulnerability risks assessment analysis. Multiple attribute decision-making problems are encountered, where a less risky alternative is chosen based on the set of risks evaluated (Samvedi et al. 2013).

Authors consider an integrated approach, where they identified and a risk index classification structure to:

- Ensure that the decision-makers follow a ‘rational’ system behaviour – utility theory (i.e., the strategy representing the utility), value functions (i.e., determining the best and the worst values), and distance to the ideal point (i.e., index representing the closeness of a specified measure to the ideal solution).
- Build the risk evaluation indexes system.
- Find the preferred solution.

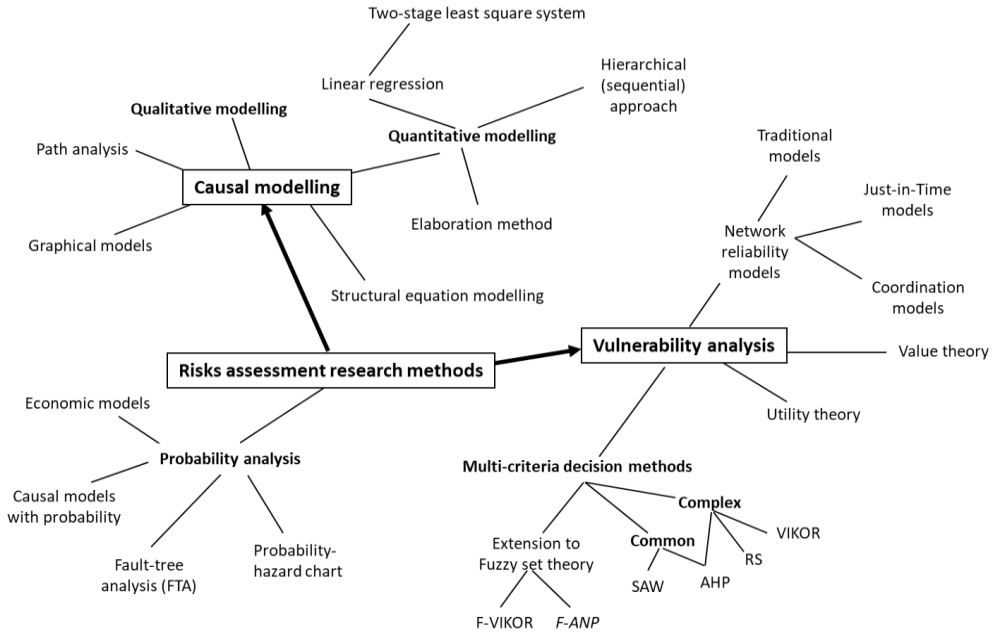
Multiple criteria evaluation methods are used to figure out which alternative has received the highest score. Numerous methods have been developed for the multiple attribute analysis of drug supply problems. Wide known methods used for

multiple attribute decision making in pharmaceutical supply chain risks assessment are, Analytic Hierarchy Process (AHP) (Ilbahar et al. 2018), Recommender Systems (RS), Simple Additive Weighting (SAW) (Jaberidoost et al. 2015), Analytic Network Process (ANP) (Yüksel and Dagdeviren 2007), Fuzzy Analytic Network Process (F-ANP) (Moeinzadeh and Hajfathaliha 2009), Multi-Criteria Optimisation and Compromise Solution (VIKOR) (Sanayei et al. 2009), Fuzzy Multi-Criteria Optimisation and Compromise Solution (F-VIKOR) (Moeinzadeh and Hajfathaliha, 2009), and others.

One type of system vulnerability analysis is the analysis of a network's reliability. Network reliability models, sometimes, consider the cost of constructing a network. The mathematical models can be used to analyse the system's reliability increase. To measure the reliability of the network, some researchers have developed models to describe its elements and activities.

Traditional models for the strategic design of network focus on cost-efficiency, not considering disruptions of inventories or supply. Just-In-Time models are assuming that every element in the network is always performing as planned, which in practice not always happens. Also, for system vulnerability analysis could be the models representing supply chain activities coordination. The summary of all the above-presented methods is shown in Figure 1.

Figure 1. *The Summary of Methods Applicable for Risks Assessment Research*



Source: Author.

Methodology

The measurement of disruption effects involves a sequence of steps as follows:

1. Risk assessment of considered products.
2. Detection of outliers and evaluation of data points.
3. An economic evaluation of lost sales.
4. The mean absolute percentage error (MAPE) indication.

Firstly, the author suggests a risk assessment method that is based on the variability of products demand. The riskiness of a considered product (*i)* is measured by a beta (β_i). It is calculated as a ratio of sales standard deviations of two products from the same category. The product with the least sales standard deviation (StD_{lr}) in the whole category (and with the least out of stocks) goes as a nominator, while a standard deviation of a considered item goes for the denominator (StD_i).

$$\beta_i = \frac{StD_{lr}}{StD_i} \quad (1)$$

It means that the medical products with low sales variability, serve as benchmarks in the categories they belong to.

The whole sample of more than 100 products, selected for testing, was divided into three categories based on the values of their betas: the highest, moderate, and low riskiness (Table 2).

Out-of-stocks were calculated for each level of riskiness, as an average percentage rate for the whole category that measures time without a product. Besides, the stock-out probability for each category level was measured as well. It indicates the percentage of products that suffer from stock-outs in the category.

Table 2. *The Levels of Demand Variability*

Values of β_i	Description	Stock-out days, %	Stock-out probability
2 = <	The highest riskiness	tbd	tbd
1.50 – 1.99	Moderate riskiness	tbd	tbd
1.00 – 1.49	Low riskiness	tbd	tbd

Source: Author.

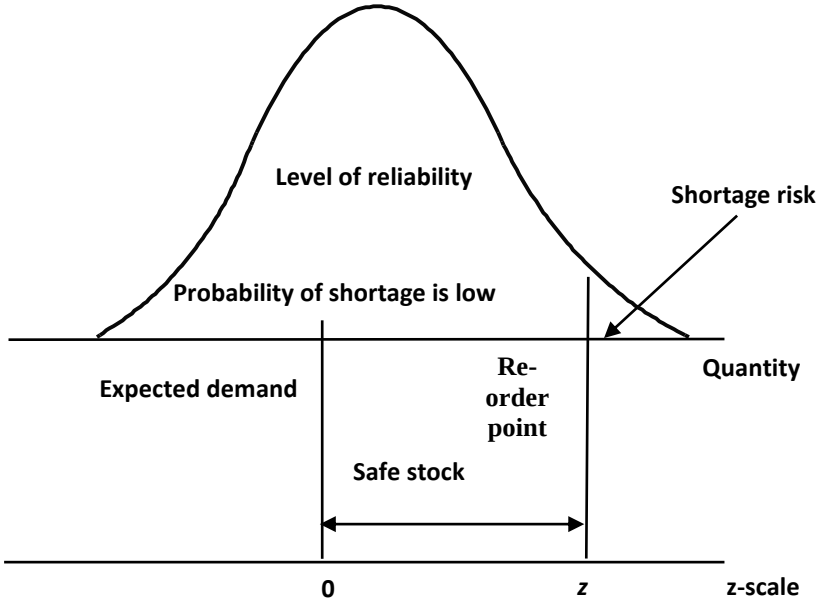
This method implies the satisfaction of an assumption of the normal distribution for each product sales (Figure 2).

At the second step, in order to estimate the disruption effect, it is necessary to get the sales pattern and gather data cleaning method. By using cleaned sales pattern, it will be possible to determine the effect size. In the study, further on lost sales estimation is generated by using cleaned data.

In general, time series method is used to forecast future demand by estimating patterns in the past, because outliers (extreme points) often distort results downwards or upwards of analysis. Due to this, every sales analysis should begin with either a graphical or statistical identification of outliers. There are various outlier test methods, like Grubbs' test (1950), Rosner's test (2011), Barnett and Lewis (1994) test, Dixon test and David test. The author uses Grubbs' test Real-life data cleaning methods for outliers' adjustment. By using the outliers'

adjustment method with a confidence level of 99% are identified outliers – exceptions, where actual sales for specific period reach standard deviation boundaries. In such cases, sales are reduced to MIN and MAX acceptable sales boundaries.

Figure 2. *The Normal Distribution and Shortage Risk*



In general, such test detects outliers from the normal distribution. The result is a probability that indicates the core data of actual sales. The outliers' test method represents the difference of the mean of the sample and the most extreme data considering the standard deviation. The test can detect one outlier at a time, with different probabilities from a data set with an assumed normal distribution.

After historical data evaluation, further steps are taken to estimate average sales per sales day.

One of the critical issues is that pharmacies do not record during a shortage. Usually, average sales per sales day prediction help to protect the data from being downwards or upwards. If a product had sales less than average sales per day and had a shortage on that day, the difference is taken for prediction and vice versa. If a product had sales higher than average sales per day and had a shortage on that day, the effect of lost sales is not calculated. For new products, which have no six weeks sales date, category average sales level per product is given.

The problem is with multiple products, which have substitution. The increase in sales of product substitute is eliminated from pre-calculated lost sales. This step is given to adjust lost sales. Adjustment of sales also could be given for season sensitive categories. Finally, the calculated lost sales in quantity are converted to value.

To estimate reached results for presented methodic MAPE indicator is used. MAPE calculation methodic is shown in Table 3. Herein, average MAPE ratio is a cumulative average calculated from the data available.

Table 3. *MAPE Calculation Methodic*

Date	Monday	Tuesday	Wednesday	Thursday	Friday
MAPE	83.293	96.071	65.47	81.339	95.217
Average MAPE Ratio	N/A	89.682	81.61133	81.54325	84.278

Source: Author.

MAPE is the indicator that presents the accuracy of methodic. It is calculated by benchmarking estimated lost sales with actual sales for products without shortage.

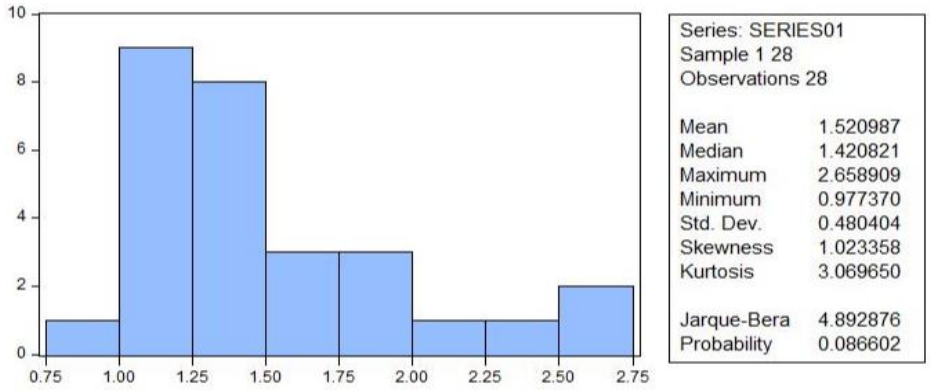
Results

The revision of disruption effects consists of several parts:

1. Risk assessment for products.
2. Detection of outliers and evaluation of data points.
3. An economic evaluation of lost sales.
4. MAPE indication.

The results are presented for each step that is performed in a particular sequence. In the *risk assessment for products* (1), the author classified products into two categories according to risk component. Then inside each category, a standard distribution analysis has been performed. This analysis presents products with demand variability component, low variability, middle variability and high variability. Figure 3 shows the results for products without shortage and Figure 4 the results for products with shortage (i.e., stock-out) cases during the period.

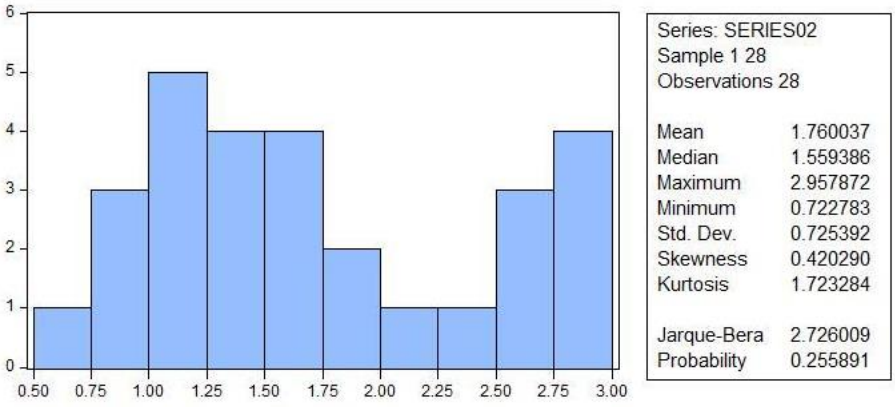
Figure 3. *The Results for Products without Shortage*



Source: Author by using EViewer Statistical Package.

According to Figure 3, the normal distribution indicates the mean of betas; for low variability demand products is 0.977, for middle variability demand products is 1.52 and for high variability demand products is 2.658.

Figure 4. *The Results for Products with Shortage*



Source: Author by using EViewer Statistical Package.

According to Figure 4, the standard deviation for low variability demand products is 0.722, for middle variability demand products is 1.76 and for high variability demand products is 2.9578.

Even the normal distribution of products is overlapping; the mean and maximum for products with shortage are higher comparing those of products without shortage.

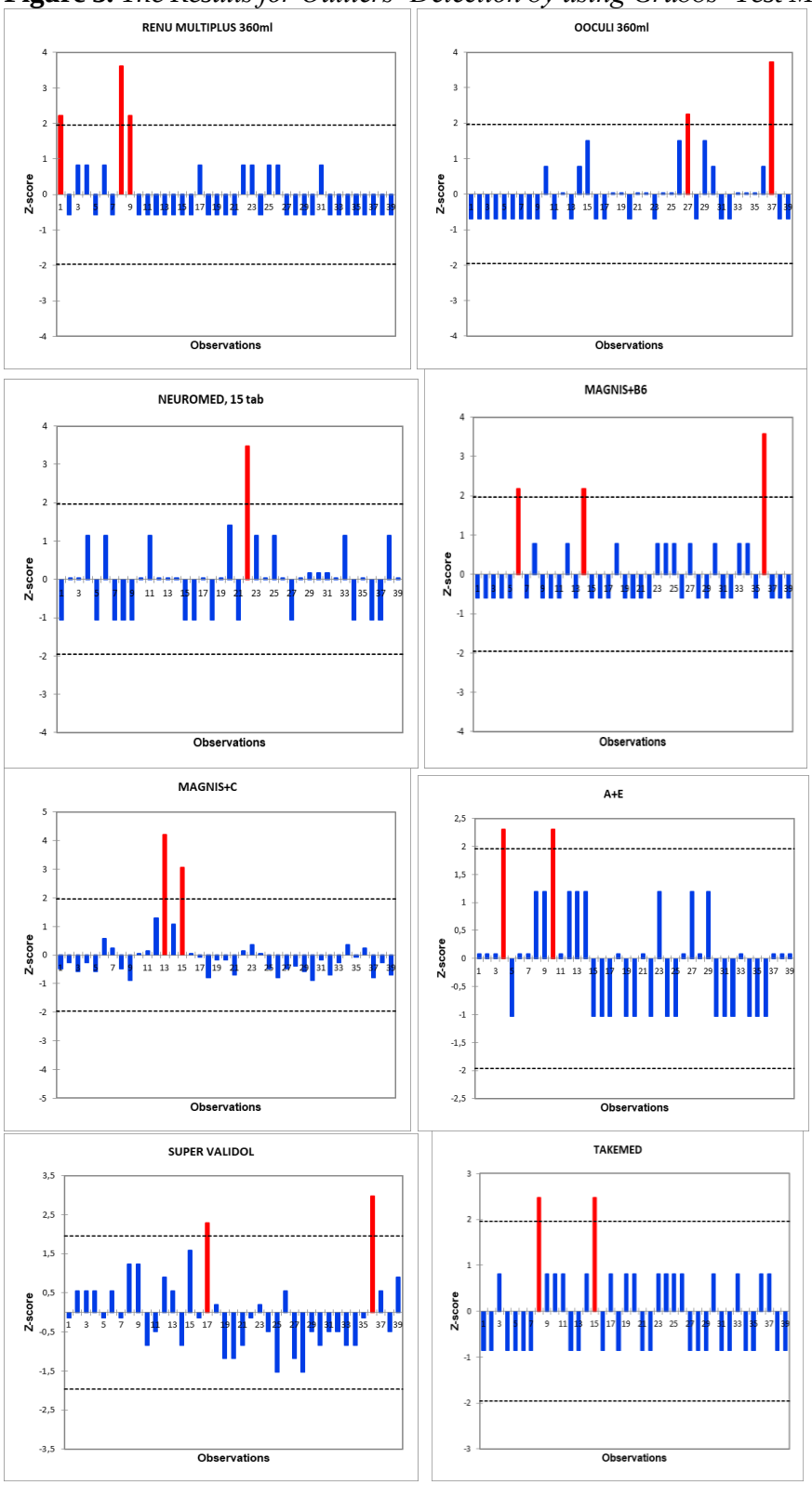
In the *detection of outliers and evaluation of data points* (2), the elimination of outliers helps to streamline sales data as for outlier case – sales points outside healthy distribution boundaries, sales data inside healthy distribution boundaries are taken. For example, the standard deviation for OOCULI 360 mL is 1.68 and Magnis+C is 2.68.

Figure 5 shows the results for the detection of outliers, which is defined using the Grubbs' test method.

Two products from 15, had no outliers detected, such as Neuromed Sleep 15 tablets and VPLAB BCAA 8:1:1. Both fall under low or middle variability demand products.

Other products had one outlier – 5 products, of which Salicilis spirit 2% 100 mL had negative z-score outlier; 2 outliers were identified for seven products and three outliers – only for two products.

Figure 5. *The Results for Outliers' Detection by using Grubbs' Test Method*



Source: Author by using the Leading Data Analysis and Statistical Solution for Microsoft Excel (XSTAT) Statistical Package.

The value of standard deviation is between 0.549 and 5.933. As during the test 40 data points have been used, the delivered normality tests present acceptable results (Table 4).

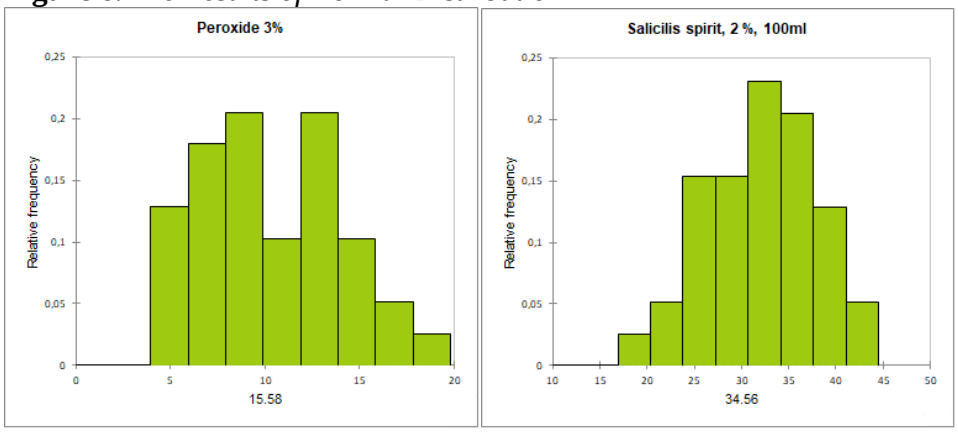
Table 4. *Results of Normality Test*

Normality test method	**Shapiro-Wilk**	**Anderson-Darling**	**Lilliefors**	**Jarque-Bera**
Result	< 0.0001	< 0.0001	< 0.0001	0.036

Source: Author by using XSTAT Statistical Package.

The normal distribution of data is well represented for Peroxide, 3% and Salicylic spiritus, 100 mL and is shown in Figure 6. Both fall under low or middle variability demand products.

Figure 6. *The Results of Normal Distribution*



Source: Author by using XSTAT Statistical Package

In the *economic evaluation of lost sales* (3), for lost sales calculation, it has been used sales-stock ratio for each sales day and its average for the period; also, average stock for the period and the number of stock-out days. The average stock is multiplied from sales-stock ratio and the number of stock-out days to get the estimation of lost sales. After the estimated lost sales are benchmarked with sales per period to get the estimation of what is the level of lost sales from total sales. The estimation for products with shortage gives 32% lost sales ratio, whereas for products without shortage is just 4%.

Finally, the author delivered the summary of results, where the number of stock-out days and probability to be in stock-out is identified.

Table 5. *Summary of Results for Products*

Values of β_i	**Stock-out Days, %**	**Stock-out Probability**	**Sales-Stock Ratio**	**Lost Sales vs Total Sales, %**
2 = <	23.35%	69.23%	4%	41%
1.50 – 1.99	15.77%	50.00%	6%	34%
1.00 – 1.49	8.10%	34.62%	10%	30%

Source: Author.

Products with a beta above 2, on average one week is on stock-out and probability to be on stock-out is 69.23%; for products with a beta below 1.5, on average less than three days are on stock-out and probability to be on stock-out is 34.62%.

In *MAPE indication*, the given methodology was applied for products without shortage. The author has randomly selected the day of stock-out, calculated lost sales and compared them with actual sales on that day. The MAPE for this exercise was 0.3867. The lower the MAPE is, the better the data performance is. The MAPE could be improved further with the application of another methodological approach.

Discussion

The author has suggested a methodology to classify products by risk and demand components. Products without shortage during month period were used for the benchmark with products, which had a shortage (i.e., stock-outs) in the defined period. Other researchers could improve the offered methodology in the area. The study has its limitations. So, future studies should expand this research application to such directions. Firstly, to the direction of risks assessment per categories analysis. Secondly, to the direction of stock-outs and demand forecast analysis. Thirdly, to the direction of analogue products selection in case of stock-outs and finally, to the decision making tools construction.

Conclusions

There are many risks in the supply chain when unexpected events might disrupt the smooth flow of drugs from producers to patients. Risk assessment topic is widely discussed and analysed; there have been identified 15 non-systematic disruption risks and 24 methods that were developed for their assessment.

The method that falls into the category of probability analysis, has been suggested. The proposed methodology aims to distinct riskier products, to determine stock-outs probabilities for products being separated into different shortage related groups and, also, to help to the estimation of disruption risks effect.

In contrast to other methods, the one suggested by the author helps to identify the groups of products that are more vulnerable to disruption risks. It shows riskier products that have a higher out-of-stock probability.

The study reveals that higher sales-stock ratio matches with products of lower disruption risk, and vice versa.

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