Pharmaceutical Sciences, 2021, 27(3), 439-449
doi:10.34172/PS.2020.93
https://ps.tbzmed.ac.ir/

Research Article

Risk Factors of Supply Chain in Biopharmaceutical Companies in Iran

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Article Info

Article History:
Received: 24 August 2020
Accepted: 8 November 2020
ePublished: 15 November 2020

Keywords:
-Biopharmaceutical
-Fuzzy screening
-Risk factors
-Risk management
-Supply chain

Abstract

Background: Supply chain risk management can help companies detect potential hazards, mitigate potential risks, and thereby increase supply chain efficiency. The biopharmaceutical industry in Iran has a generic-based pharmerging market. Therefore, identifying risks associated with the supply chain of those drugs can significantly boost the possibility of success of biopharmaceutical companies. This study is conducted to determine the supply chain risk factors of biopharmaceuticals companies in Iran.

Methods: The current research work is a qualitative-quantitative study. A systematic review and interview with experts (n=14) were conducted to identify potential supply chain risks in the biopharmaceutical industries. To determine the significance of identified risks, Fuzzy screening method was employed to collect the opinions of experts (n=16) in the biopharmaceutical industries.

Results: By systematic review and interviews with the biopharmaceutical industry experts, 100 potential risks in the biopharmaceutical industry supply chain were identified. These risks were divided into two general categories namely macro and micro risks. Based on experts' judgment, 77 out of 100 identified risks were eliminated and 23 significant risks were determined. The most important risks are the Ministry of health (as the regulatory body) conflict of interest, US sanctions, lack of domestic suppliers of essential materials, pseudo-productivity, and money transfer related to the bank's sanctions.

Conclusion: Due to the multitude of present risks and the impossibility of controlling all of them, it is recommended that managers and producers focus more on controlling the identified significant risks.

Introduction

Risk is represented in terms of uncertain events which possess the likelihood of unfavorable outcomes such as late delivery, financial burdens, loss of business, etc.[1,2] Supply chain risk is defined as 'the likelihood and impact of unexpected macro and/or micro-level events or conditions that adversely influence any part of a supply chain and lead to operational, tactical, or strategic level failures or irregularities.[3]

In contrast, supply chain risk management seeks to reduce risk and uncertainty in the supply chain by mitigation strategies. Therefore, it is important to identify, evaluate, and classify all possible risks to be able to monitor the probability and impacts of unfortunate events.[4] According to the Supply Chain Management Professional Council, the planning and management of all sourcing, delivery, and logistics activities involved in a supply chain, are considered as supply chain management.[5]

Medicine quality and efficiency are two of the health-care programs' main objectives. Pharmaceutical manufacturers have an important role in achieving these objectives. Nevertheless, they usually need to survive in a complicated environment where they face uncertainties that can affect their performance, as well as medicines' accessibility and safety. Risk management is a new approach for assessing and managing such uncertainties.[6,7] Therefore, supply chain risk management should be an essential part of the strategy of pharmaceutical companies as it is tightly connected to both preserving resources and saving patients' lives by increasing the accessibility to the required medicine.[8,9] That is even more significant in biopharmaceutical industries where the costs of production, ranging from developing new medicine to licensing, are greater than

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that of regular pharmaceutical companies which makes Biopharmaceutical industries subject to more risks and subsequently in greater need of implementing risk management strategies.[10]

The importance of the mentioned subject has been further endorsed by Fawcett *et al.*[12] where it is emphasized that the awareness of supply chain risk, encourages managers to perform the supply chain operations in a competitive manner.[11] In addition, there are research works that have explored mechanisms to overcome serious supply chain risks and to improve their performance accordingly.

The biotechnology industry has experienced considerable growth in recent years so that just between 2004 and 2014 its size has doubled. Judging based on the worldwide sale of prescription medicine and those over-the-counter pharmaceuticals, biopharmaceuticals have accounted for over twenty-four percent of the world drug market in 2015, while it is expected to reach twenty-nine percent by 2022. In the past two decades, some Iranian companies have started manufacturing biosimilars. They have provided Iran's pharmaceutical market with biopharmaceuticals worth $220m in just 2015. Today, in addition to the institutes and corporations manufacturing life medical products, there are eighteen private biopharmaceutical firms that produce biosimilars approved by the ministry of health (MOH).[13,14] No doubt, supply chain risk management is crucial to Iranian biopharmaceutical industries' operational excellence. However, so far no research in the Iranian biopharmaceutical industries has been conducted in addressing the issue. The present study, therefore, aims to detect and evaluate the above-mentioned risks in the Iranian biopharmaceutical supply chain. Objective of the study was Identifying the supply chain risk factors specific to the Iranian biopharmaceutical and evaluating and classifying supply chain risk factors involved in the Iranian biopharmaceutical by using fuzzy screening.

Methods

This study was done in an organized step-by-step process. The first step was taken to identify the possible risks in the supply chain of the pharmaceutical industry in a general scene where its results were employed to obtain those risks specific to the Iranian biopharmaceutical industry. In the third step, the risks recognized in the previous stages were refined while comparing with the expert's opinion.

First step: This systematic review was conducted using a predefined protocol in accordance with the MOOSE (meta-analysis of observational studies in epidemiology) checklists.[15,16]

We systematically searched in PubMed, Ovid, Web of Science, Scopus, Google Scholar, and Embase databases for articles published on or before May 1st, 2019. We used the following keywords:

("risk management" OR "risk assessment") AND ("supply chain" OR "production") AND ("*pharmaceutical" OR "biomedicine" OR "biotechnology"). (Appendix 1 in supplementary data)

The keywords were limited by specialized perspectives, for concentrating on the objectives of the study and preventing divergence.

In the present work, we tried to just consider the original and the most reliable documents that have assessed medicine supply chain risks. Two authors went independently through the collected documents and ruled out unrelated reports based on strict criteria and screened the title and the abstract of the retrieved articles. A three-step approach was followed to select the target documents.

First, the results screened by their titles and irrelevant results were excluded. Second, the abstracts of the selected results were reviewed to eliminate conference abstracts, practice guidelines, editorial letters, or reviews. Third, the full texts of the selected studies were reviewed separately.

Then, two authors held a face-to-face meeting to discuss their results and narrow down the differences in opinions and when necessary, a third author was invited to avoid selection bias.

To include a study, a consensus of opinion was reached by at least two reviewers. Eventually, the full texts of the included articles were double-checked and those out-

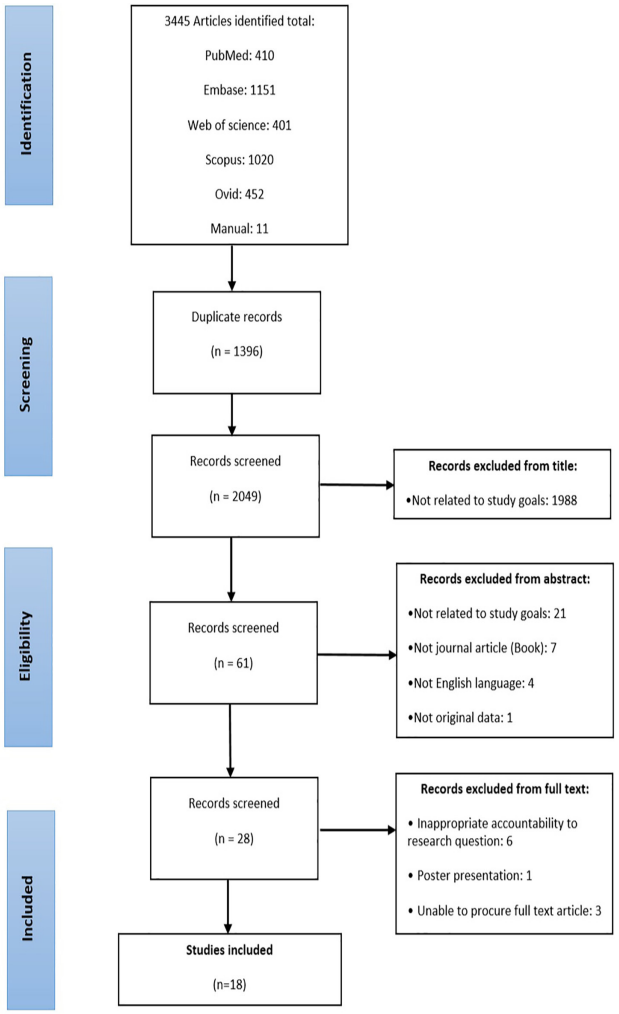

Figure 1. MOOSE flow diagram of observational studies included in the systematic review.

of-scope articles were removed. This process is shown in Figure 1.

For the quality assessment of documents, two reviewers used a checklist of the quality of cross-sectional studies (AXIS).[17] Finally, the requested data were extracted and summarized in the data-sheet.

Second step: Considering the impact of socio-economic and socio-cultural conditions on the supply chain of biological medicines, the researchers conducted semi-structured interviews with 14 experts in the biopharmaceutical industry who had at least five years of experience in biopharmaceutical industry management at the date of the interview. In order to cover various types of viewpoints in Iran's biopharmaceutical industry, the interviewees were chosen from different companies and organizations. During the interviews, the participants were asked about other risks that are specific to the Iranian biopharmaceutical supply chain. At this stage, the sample reached 14 individuals due to data saturation.(Appendix 2)

Third step: In order to rank the identified risks, in the third step of the study, after pooling of risks, the risks were classified into micro and macro according to the study of Ho *et al.*[3] Next, we used the Fuzzy screening method. It is noteworthy to know that Fuzzy screening is useful for the selection of a small subset of alternatives from a much larger set of them.[18] This method provides a reliable approach for applying criteria in selecting items. It is easy to implement while it gives a chance for all criteria (in our case expert opinions) to be reflected in the final results of a given investigation. To apply the above-explained method in this research work, sixteen experts in the biopharmaceutical industries, including CEOs, supply chain managers, and production managers, were asked to rate the identified risks in terms of their importance (very important, important, medium, low, and non-significant) on a Likert scale according to Iran's conditions.

The process is summarized below:

1- Organizing expert opinions collected from questionnaires into estimates, and making the triangular fuzzy number as follows:

$$MA = \sqrt[n]{\prod_{i=1}^{n} X_{A\,i}}$$

TFN = (L_A , M_A , U_A)

L_A= Min (X_{Ai})

where i denotes the *i*th expert, I=1, 2, …, n, and U_A=Max (X_{Ai})

X_{Ai} denotes the appraisal value of the *i*th expert for criterion A; L_A denotes the bottom of all the experts' appraisal value for criterion A; M_A denotes the geometric mean of all the experts' appraisal value for criterion A and U_A denotes the top of all the experts' appraisal value for criterion A.[19]

2- Since the importance of all indicators is fuzzy values, therefore, it is essential to calculate a non-fuzzy value by defuzzification method. In other words, defuzzification is a technique to convert the fuzzy number into crisp real numbers. A triangular fuzzy number can be defuzzified to

$$M_{CRISP} = \frac{(4m+l+u)}{6}$$

a crisp number as follows:

Finally, appropriate indicators could be screened out from abundant indicators by setting the threshold M_{CRISP}. Following Pareto's law, this study also set the threshold and eliminated factors that had a geometric mean below α> 80%. The following operations were performed to obtain the threshold at each of the outputs.[20-22]

1. Obtaining minimum and maximum crisp number for all factors.

2. Acquiring a domain using the following formula:

D= Defuzzy max - Defuzzy min

3. Earning threshold using the following formula:

$\alpha = D \times 0.8$

$\alpha = (4.87 - 1.12) \times 0.8 = 3$

The principle of screening is as the following:

If $M_{CRISP} \geq \alpha$, then this risk is accepted as an important risk.

If $M_{CRISP} < \alpha$, then this risk is not important.

Results

Characteristics of included studies

From the online database, 3445 records were retrieved. By eliminating duplicates documents, 2049 articles were reviewed, and among them,18 articles that met the inclusion criteria, were included in this study. The quality of the included studies assessed by the checklist of the quality of cross-sectional studies (AXIS).[17] Likewise, the risk of bias within each included study was assessed based on the unclear objective, unjustified sample size, undetermined statistical significance, incomplete outcome data, and non-described respondents with ratings of "low risk of bias," "high risk of bias," and "unclear" (uncertain risk of bias). We did not see a high risk for bias types (selection, reporting, performance, and attrition) in 18 included articles (Table 1).

Among the mentioned eighteen studies which have been published between 2005 and 2019, seven of them were about risk assessment, six of them were about risk mitigation, and three studies were done on risk identification. Additionally, the risk evaluation of the medicine supply chain was explored in two cases. Finally, a multi-phase study has been done on risk assessment and risk mitigation simultaneously (Table 2).

Risks extracted from literature

Overall, 84 risks of the supply chain were extracted from the available research works. The risk of information flow disruption had the highest frequency (ten times) among the studies. The regulation and issues related to regulatory agencies and the transportation risk had the second-highest frequency where they were repeated nine times. The operational issues, supply and supplier issues, inappropriate trading partnership networks and quality issues were the mentioned risks with eight frequencies. The

Table 1. Quality assessment of 19 studies by checklist of the quality of cross-sectional studies (AXIS).

1	Were the aims/objectives of the studies clear?	Yes
2	Were the studeis design appropriate for the stated aim(s)?	Yes
3	Were the sample sizes justified?	Yes
4	Were the target/reference populations clearly defined?	Yes
5	Were the sample frames taken from an appropriate population base so that they closely represented the target/ reference populations under investigation?	Yes
6	Were the selection process likely to select subjects/participants that were representative of the target/reference populations under investigation?	Yes
7	Were measures undertaken to address and categorise non-responders?	Yes
8	Were the risk factor and outcome variables measured appropriate to the aims of the studeis?	Yes
9	Were the risk factor and outcome variables measured in studies correctly using instruments/measurements that had been trialled, piloted or published previously?	Yes
10	Are they clear what were used to determined statistical significance and/or precision estimates? (e.g. p-values, confidence intervals)	Yes
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated in studies?	Yes
12	Were the basic data adequately described in studies?	Yes
13	Does the response rate raise concerns about non-response bias in studies?	No
14	If appropriate, were information about non-responders described in studies?	Yes
15	Were the results internally consistent in studies?	Yes
16	Were the results presented for all the analyses described in the methods?	Yes
17	Were the authors' discussions and conclusions justified by the results?	Yes
18	Were the limmitations of the each study discussed?	Yes
19	Was there any funding sources or conflicts of interest that may affect the authors' interpretation of the results in the each study?	No
20	Was ethical approval or consent of participants attained in each study?	Not applicable

Table 2. Attributes of the studies entered into the study.

Authors	Year	Scope	Place	Main results
Nilay Shah[23]	2004	Risk Mitigation	UK	Supply chain risks were identified. Production capacity and planning, communication network design, and production site design were explored.
Vrassidas Leopoulos, *et al*[24]	2005	Risk identification	Greece	Risks identified in the proposed electronic model among Greek pharmaceutical companies.
Liz Breen[25]	2008	Risk evaluation	UK	The 17 risks in the pharmaceutical supply chain were identified and prioritize.
Chris Enyinda, *et al*[26]	2009	Risk Mitigation	US	The most significant risks including regulatory risk, business risk, and technical risk were highlighted.
Mauricio Blos, *et al*[27]	2010	Risk Mitigation	Taiwan	Twelve supply chain risks were identified that could be resolved with the business planning models.
Chris Enyinda, *et al*[28]	2010	Risk Mitigation	UAE	Counterfeit, Food and Drugs Board, fluctuation in currency rate, and finally supplier failure were considered as major supply chain risks**.**
Carl Henning Reschke[29]	2010	Risk identification	Denmark	Market, regulatory, and R&D risks and mergers are important.
Philip Kaminsky, *et al*[30]	2012	Risk Mitigation	US	The most critical risks in the supply chain were considered as follows: reassuring production, product contamination, the supply of raw materials, outsourcing risks, forecasting error, risks to regulatory agencies, and infringement of intellectual property rights.
Kamath, *et al*[31]	2012	Risk assessment	India	The most critical risks, from more important to less important, are regulatory, financial, and warehousing.
Gholamhossein Mehralian, *et al*[32]	2012	Risk assessment	Iran	A total number of 37 risks have been identified in the area of supplier selection and have been classified into nine groups. Delivery factors have been considered as the highest priority, and then cost, and quality risk groups were given the next priorities.
Lhoussaine Ouabouch, *et al*[33]	2013	Risk evaluation	Morocco	The most critical supply chain risks, from more important to less important, are supplier inability, inventory shortages, rising raw material prices, and supplier quality issues.

Table 2. Continued.

Mona Jaberidoost, *et al*[34]	2015	Risk assessment	Iran	Half of the total risks in the pharmaceutical supply chain are internal risks that can be resolved internally by companies. The political situation and the associated risks also force companies to focus more on financial and supply management.
Vinayak Vishwakarma, *et al*[35]	2016	Risk assessment	India	The twenty-four identified risks in the Indian supply chain were categorized into five classes, including financial, logistics and network risks, market and government-related risks, and strategic risks.
Fahian Huq, *et al*[36]	2016	Risk assessment & Risk mitigation	UK	The five main factors that give rise to the disruption in the supply chain are quality defects, unforeseen and accidental interruptions in production processes, order processing problems, timely delivery of products, and mismatches between market and supplier requirements.
Nina Bucalo, *et al*[37]	2017	Risk identification	Slovenia	The existing risks and their importance in the distribution processes of pharmaceutical companies in Slovenia were identified.
Chatchai Raka, *et al*[38]	2017	Risk assessment	Thailand	The most important risk is the regulatory risk that is followed by information, operational, financial, intellectual property, market, and technology risks.
Chris Enyinda[39]	2018	Risk Mitigation	UAE	Supply chain managers place great importance on regulation/legislation, followed by operational and reputation risks, while they think that financial, market and related risks are less important.
Abdul Moktadir, *et al*[40]	2018	Risk assessment	Bangladesh	Supply-related risks, such as import fluctuation, lack of information sharing, the inability of the primary supplier, and lack of access to raw materials, are prioritized over operational, financial, and demand-related risks.

risks of natural disasters and terrorism, financial problems and currency fluctuation have been repeated seven times. Finally, inventory management were mentioned six times. As shown in Table 3, most other risks have been identified

Table 3. Reported research works on "risks" and their frequencies.

Risks	Frequency in studies
Information flow disruption[24,27,32-38,40]	10
Regulation and regulatory agencies issues[25,26,28-31,34,38,39] - Transportation risk[25,27,31-33,35,37,39,40]	9
Operational issues[23,25-27,34,37-39] - Supply and supplier issue[25,27,30,32,34,35,37,40] - Inappropriate trading Partnership network[24,26,27,32,33,35,36,39] - Quality issues[24,30,32-34,36,37,40]	8
Natural disasters and terrorism[25,27,30,32,35-37] - Financial problems[24,31,32,37-40] - Currency fluctuation[28,32,34,35,37,39,40]	7
Inventory management[23,25,27,33,35,37]	6
Unforeseen and random interruptions in manufacturing processes[30,33,35-37] - Quality of skills, education level and talent of the labor force[25,32,34,36,37] - Demand fluctuations[23-25,35,40] - Inaccurate demand forecasting[30,33,34,36,40] - Untimely delivery of products[30,32,33,36,37]	5
Raw materials supply[30,35,37,40] - Limited suppliers[25,32,34,37] - Counterfeit[25,28,31,35] - R & D expenses[23,29,35,39] - Strategy issues[27,29,34,37]	4
Consumers taste changes[23,32,37] - Political instability[32,35,36] - Unplanning[23,25,27] – Contamination[30,37,40] - Organization and process issues[23,24,27] – Competition[24,34,40] - Government policy fluctuation[24,34,35] - The risk of infringement of IPR[26,36,38] - Change in legislation and policies[34,37,39] - Interest rate[32,34,40] - Cash flow[25,34,37] - Purchasing cycle time[27,34,37] - Raw material price[33-35] - The undesirable quality of raw material[27,32,34] - Key supplier failure[28,33,40]	3
Continuous supply timely[30,33] - Supplier inflexibility[27,35] - Reliability of energy[36,40] - Inappropriate contract and agreements[25,32] - Technology level[32,38] – Sanction[32,34] - Payable Tax change[32,35] - Pricing policies[34,35] - Production cost[32,37] - Machine, equipment or facility failure[37,40] - Reputation risk[32,39] - Time to market[27,34]	2
Myopic vision[35] - Dependence on alliance partners[24] - Outsourcing related risk[30] - Tariff policies changes - Inappropriate storage - Waste management - Inflexibility in product variety - Inflexibility in quantities - Delivery reliability - Inflexibility in delivering - Environmental hazards - Technology development problems[32] - Lack of managerial knowledge - Human errors - Motivation - inappropriate location - Formulation development problems - Inappropriate production process and technology - New competitors (new medicine or new company) - Banking regulation instability - Lack of regulation transparency - Commercial regulation – Lobbying risks in the decision-making process - Biased interpretation of regulations - Product selection - Inappropriate distribution and coverage Economic stagnation - Money transfer - Inflation rate - Long cash collection cycle - Return of investment[34] - Merging and acquisition[29] - Customer services disruption[27] - Fragmentation[25] - Capital/fund management[35] – Theft of goods[37]	1

or studied only once.

Risks identified by interviewing biopharmaceutical industry experts

In addition to the risks extracted from the studies, sixteen additional risks were found in the biopharmaceutical supply chain through interviews with biopharmaceutical industry experts in Iran. These risks are as below:

Lack of domestic supplier of critical material, defect of international vision, business development issues, single actor in the biopharmaceutical industry, international certification issues, pseudo-productivity (repacking), drug list limitation, low international trading experience, dual exchange rates, low trust in domestic products, international marketing issues, MOH (Ministry of health) conflict of interest, long-term licensing process for clinical trials, lack of standard CROs for clinical trials and lack of efficient structure for technology transfer.

Thus, in total, 100 risks were identified for the supply chains.

Risk classifications

Generally, the risks are divided into two types of micro and macro. Some of the macro risk factors are risks of MOH conflict of interest, sanctions, political instability, the long-term licensing process for the clinical trial, lack of standard CROs for the clinical trial, lack of efficient structure for technology transfer, and natural disasters & terrorism.

On the other hand, micro risk factors include supply, demand, manufacturing, regulation, logistics, and financial.

The importance of these risks from the Iranian biopharmaceutical industry experts' point of view, is shown in Table 4.

Significance of risks

As shown in Table 4, Iran as a developing country in the biopharmaceutical industry, is facing various risks. According to the experts in the field, the most important risks to the industry are MOH conflict of interest, sanctions, pseudo-productivity, the lack of domestic supplier for essential materials, and money-transfer problem which had a score higher than 4.

Discussion

This study aims to provide the first comprehensive assessment of Iranian biopharmaceutical supply chain risks. Reviewing studies and interviews with biopharmaceutical industry experts resulted in identifying 100 potential risks in the biopharmaceutical industry. Based on the expert's opinion, 23 out of 100 of the found potential risks were pointed as those with more importance in the Iranian biopharmaceutical industry supply chain. These findings extend our knowledge of the Iranian biopharmaceutical community as a growing industry. In the last two decades, Iran has become a pioneer in the biomedicine market in the Middle East and North Africa. While in Asia, Iran lies in the second position from the market capacity point of view, after India. Some Iranian biopharmaceutical firms have entered into international markets like Turkey and Russia.[41,42] Accordingly, investigations shows that the number of domestically produced biosimilars has toped to 32 in 2020.

Risks related to macro factors indicate fundamental and structural risks in the biopharmaceutical supply chain. Iranian ministry of health has both the role of purchaser and supervisor, as well as the role of policymaker and price setting for medicines.[43] From the medicine producers' perspective, playing simultaneously the main role in all mentioned areas by the ministry of health poses a threat to the pharmaceutical industry of Iran. In recent years, Iran has been subject to financial and non-financial sanctions by the international community and the United States, and like other industries, the biopharmaceutical industry is at risk in this respect.[44,45] Therefore, it seems natural that sanctions are one of the major risk factors in the biopharmaceutical industry. Jaberidoost *et al*. have also identified sanctions as one of the most important risks in the pharmaceutical supply chain in Iran.[34] Since there is no long-term plan to terminate the mentioned risk in the Iranian pharmaceutical and biopharmaceutical industry,[46] so, it is not surprising that political instability is one of the major risks in the biopharmaceutical industry in Iran.

The strategy of medicine production in Iran has been based on the needs of the Iranian people, and the export of medicines has not been much emphasized. Therefore, structures in the Iranian biopharmaceutical industry are limited to national standards which are rather at a lower level comparing to that of international standards.[47] The mentioned problems in the Iranian biopharmaceutical industry are in line with the results of Moradi *et al* that have recently been published where the lack of technology, equipment, and development are pointed out as important risks of supply and production chain in the biopharmaceutical industry.[48]

Pseudo-productivity is the most critical regulatory risk in the biopharmaceutical industry in Iran. As some biopharmaceutical companies import and repack biological drugs as domestic products while they exploit governmental support that is offered as subsidized foreign currency by the Iranian government in an effort to give a boost to the domestic industries. This creates an unfair competitive environment for the companies that produce from scratch at the cellular level and expose them to the risk of pseudo-productivity.

Pharmaceutical regulations also undergo minor or major changes when governments and Food and Drug administration officials are replaced. This means that there are many regulatory requirements that are subject to continuous change which causes a non-stable atmosphere in the related companies.[49] Therefore, regulatory risks are critical and potentially high-frequent risks in the Iranian biopharmaceutical industry, this is highlighted in research performed by Jaberidoost *et al.*[34] In many other studies

Table 4. Iranian biopharmaceutical industry supply chain risk fuzzy screening with scores.

Category	Risk	Selected/ Rejected	Category	Risk	Selected/ Rejected
Supply factors	Lack of domestic supplier of essential materials	4.43 (S)	Manufacturing factors	Machine, equipment or facility failure	2.57 (R)
	Purchasing cycle time	2.94 (R)		R and D issues	2.50 (R)
	Quality issues	2.92 (R)		Unplanning	2.43 (R)
	Limited suppliers	2.78 (R)		Production cost	2.43 (R)
	Raw material supply	2.61 (R)		Reputation risk	2.43 (R)
	Supply and supplier issue	2.45 (R)		Quality of skills, education level and talent of the labor force	2.43 (R)
	Inappropriate trading partnership network	2.30 (R)		Inappropriate production process and technology	2.43 (R)
	Continuous supply timely	2.26 (R)		Unforeseen and random interruptions in manufacturing processes	2.36 (R)
	Delivery reliability	2.21 (R)		Operation issues	2.29 (R)
	Fragmentation	2.21 (R)		Strategy issues	2.21 (R)
	Untimely delivery of products	2.19 (R)		Dependence on alliance partners	2.21 (R)
	Undesirable quality of raw material	2.15 (R)		Formulation development	2.21 (R)
	Reliability of energy, internal transport and telecommunication infrastructure	2.11 (R)		Inventory management	2.21 (R)
	Key supplier failure	2.02 (R)		Competition	2.21 (R)
	Break in information flow	1.99 (R)		Myopic vision	2.07 (R)
	Inappropriate storage	1.82 (R)		Organization & process issues	2.07 (R)
	Technology level	1.80 (R)		Environmental hazards	2.00 (R)
	Supplier inflexibility	1.70 (R)		Merging and acquisition	1.93 (R)
	Waste management	1.65 (R)		Inappropriate location	1.93 (R)
	Inflexibility in product variety	1.64 (R)		Contamination	1.93 (R)
	Inappropriate contract and agreements	1.59 (R)	Regulatory factors	Pseudo producity (repacking)	4.30 (S)
	Inflexibility in Delivering	1.59 (R)		Drug List Restrictions	3.83 (S)
	Raw material price	1.40 (R)		Government policy fluctuation	3.55 (S)
	Inflexibility in quantities	1.40 (R)		Pricing policies	3.51 (S)
Manufacturing factors	Defect of international vision	4.21 (S)		Biased interpretation of regulations	3.47 (S)
	Business development issues	2.93 (R)		Banking regulation instability	3.44 (S)
	New competitors (new medicine or new company)	2.86 (R)		Lack of regulation transparency	3.39 (S)
	Single actor in the biopharmaceutical industry (exclusivity)	2.79 (R)		Lobbying risks in the decision-making process	3.37 (S)
	Outsourcing related risk	2.79 (R)		Change in legislation and policies	3.20 (S)
	Motivation	2.79 (R)		Commercial regulation	2.96 (R)
	Human errors	2.71 (R)		Long-term licensing process for stablishing clinical trial	2.93 (R)
	Time to market	2.71 (R)		Regulation and regulatory agencies issues	2.90 (R)
	Lack of managerial knowledge	2.71 (R)		Law knowledge of International Regulations	2.85 (R)
	international certification issues	2.71 (R)		Diversity in governmental agencies	2.78 (R)
	Technology development problems	2.57 (R)		Risk of infringement of IPR	2.37 (R)

Table 4. Continued

Financial factors	Money transfer	4.07 (S)
	Long cash collection cycle	3.93 (S)
	Inflation rate	3.93 (S)
	Dual exchange rate	3.71 (S)
	Cash flow	3.71 (S)
	Currency fluctuation	3.57 (S)
	Interest rate	3.57 (S)
	Financial problems	3.36 (S)
	Economic stagnation	3.21 (S)
	Tariff policies changes	3.14 (S)
	Return of investment	2.93 (R)
	Capital/fund management	2.93 (R)
	Tax payable change	2.43 (R)
Logistic factors	Counterfeit	2.18 (R)
	Transportation risks	1.85 (R)
	Theft of goods	1.12 (R)
Demand factors	Law trust in domestic product	2.91 (R)
	Marketing issues (international level)	2.58 (R)
	Demand fluctuations	2.53 (R)
	Inappropriate distribution and coverage	2.27 (R)
	Inaccurate demand forecasting	2.26 (R)
	Product selection	2.18 (R)
	Customer services disruption	2.18 (R)
	Consumers taste changes	1.97 (R)
Macro factors	MOH conflict of interest	4.15 (S)
	Sanction	4.87 (S)
	Political instability	3.40 (S)
	Lack of standard CROs for clinical trial	2.55 (R)
	Natural disasters and terrorism	2.25 (R)
	Lack of efficient structure for technology transfer	2.50 (R)

conducted around the world, regulatory factors have been considered as important and effective risks for the drug supply chain.[25,26,28-31,34,38,39] In another investigation done by Enyinda *et al.*[26], regulatory risks were considered as the most critical risks of the pharmaceutical supply chain.[26]

It should be noted that since Iran is not a member of the WTO, international and domestic copyright, patent, and copyright laws are not taken seriously.[46,50]

The most important risk factor among the financial factors is the risk of money transfer related to the bank's sanctions for importing raw materials and exporting biopharmaceutical products of the industry.[34,51] Iranian general economic conditions have not been satisfying as the inflation and exchange rates for Iranian Rials against foreign currencies have been in sharp flux over recent years.[52] Having that in mind, it is not surprising to see that from the perspective of biopharmaceutical industry experts the financial factors are considered as critical risks that are reflected in the current study. Similarly, Raka *et al.* in 2017 have shown that financial risks are one of the critical supply chain risks in Thailand.[38]

No doubt, there are various risks that can affect the supply chain factors in the biopharmaceutical industry; among them, the risk originating from the lack of domestic suppliers of essential materials is very significant since most of the pharmaceuticals in developing countries, particularly biological drugs are imported from abroad while the number of domestic suppliers is low. This risk is also classified as a significant risk according to a study done by Jabridoost *et al.*[34]

In the present research, it is shown that demand-related risks are mostly linked to low trust in domestic products, marketing issues particularly at the international level, and demand fluctuations. As it is well-known, cultural and social conditions on one hand and the emerging biopharmaceutical industry on the other hand are the two main sources of this risk.[53]

Although various studies have shown that government support for the domestic industry has been followed by risk reduction in the supply chain of the sponsored industry.[53,54] However, there are other studies where the support risk has been considered as a significant risk in the biopharmaceutical supply chain.[38,55]

Action plan

According to the results of investigations, the Iranian pharmaceutical industry is mostly faced with external risks. Therefore, in order to reduce the effects of the mentioned challenges and revitalize the industry, the government needs to take necessary measures under a comprehensive plan. We recommend the following measures to be taken.

- To reduce the regulatory risk, close cooperation between the ministry of health as the regulator body and biopharmaceutical companies is urged to be established in making policies in main issues such as pricing, registration of new drugs to the national drug list, etc.
- Establishing a responsible and effective management system in pharmaceutical sector and guaranteeing that there is no conflict of interest.
- The knowledge-based companies should be supported to make sure that the required raw materials in the biopharmaceutical industry are adequately available.
- Increasing transparency in the decision-making process to ensure effective governance in medicine indicators.

- Financially supporting biopharmaceutical companies by allocating lines of credit and granting low-interest loans to help them develop and reduce their finance costs due to the long cash collection cycle.

Also, to help companies lower the risks originating from their internal structures, it is necessary to develop programs specific to each company to increase their internal efficiency in facing challenges particularly the uncertainty in their supply chain.

Conclusion

In this study, we have identified the biopharmaceutical supply chain risks. We have also evaluated all potential risks in the biopharmaceutical industry supply chain by fuzzy screening in close consulting with the known experts of the field. Among all those investigated risks, the following five risks, according to the Iranian biopharmaceutical industry experts, can have a more significant impact on the biopharmaceutical supply chain. They are namely MOH conflict of interest, sanctions, lack of domestic supplier of essential materials, pseudo-productivity, and the money-transfer problem related to bank's sanctions. The results of our research show that the Iranian biopharmaceutical industry and supply chain have been affected by the political-economical conditions. Therefore, in order to achieve a sustainable biopharmaceutical supply chain, the Iranian government needs to take action and step in by offering supporting programs to revitalize the companies involved in the supply chain.

For a more precise assessment of biopharmaceutical supply chain risks, this research can be extended in analyzing risk by using qualitative and quantitative methods. For example application of FCM (fuzzy cognitive mapping) & fuzzy FMEA (failure mode and effects analysis) to modeling biopharmaceutical supply chain risks.

Acknowledgments

This study was part of Hadi Abbasian PhD thesis registered in Tehran University of Medical Sciences.

Ethical Issues

The study was confirmed by the Ethics Committee of Tehran University of Medical Sciences (TUMS): IR.TUMS.VCR.REC.1397.675.

Author Contributions

HA: Conception, search databases, extracted data, analysis, writing of manuscript; RY: analysis and contributed in preparing original draft. AA and MS: contributed in preparing original draft. MT search databases and extracted data. SN: search databases, extracted data, and revision of the manuscript. AK: Conception, design of the study and supervised all processes. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Data

Supplementary file is available on the journal's web site along with the published article.

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