Risk factors of supply chain in biopharmaceutical companies in Iran

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Running title: Iranian biopharmaceutical supply chain risks

Abstract:

Introduction: 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.

Keywords: Biopharmaceutical, Supply chain, Risk factors, Risk management, Fuzzy screening.

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 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. (2012) 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.[12]

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:

- Identifying the general supply chain risk factors involved in the biopharmaceutical.
- Identifying the supply chain risk factors specific to the Iranian biopharmaceutical.
- 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)

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-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 William et al. (2015).[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:

$$TFN = (L_A , M_A , U_A)$$
$$L_A = Min (X_{Ai})$$
$$MA = \sqrt[n]{\prod_{i=1}^{n} X_{A_i}}$$

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

And 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 a crisp number as follows:

$$M_{CRISP} = \frac{(4m+l+u)}{6} \quad 20$$

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.[21,22]

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

2. Acquiring a domain using the following formula:

$$D = \text{Defuzzy max} - \text{Defuzzy min}$$

3. Earning threshold using the following formula:

$$α = D * 0.8$$

$$α = (4.87 - 1.12) * 0.8 = 3$$

The principle of screening is as the following:

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

If $M_{CRISP} < α$, 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).

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.
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 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 risks of natural disasters & 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 or studied only once.

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

Risks	Frequency in studies
Information flow disruption[24,27,32-38,40]	10
Regulation & 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 & 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 & 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 & policies[34,37,39] - Interest rate[32,34,40] - Cash flow[25,34,37] - Purchasing	3

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]

Continuous supply timely[30,33] - Supplier inflexibility[27,35] - Reliability of energy[36,40] - Inappropriate contract & 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 & 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

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 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. (2009), 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.

Conflicts of Interest Disclosure:
Authors declare that they have no conflicts of interest.

References:

1. Holton GA. Defining risk. Financial analysts journal 2004;60(6):19-25. doi: 10.2469/faj.v60.n6.2669

2. Mangla SK, Kumar P, Barua MK. An integrated methodology of fta and fuzzy ahp for risk assessment in green supply chain. International Journal of Operational Research 2016;25(1):77-99. doi: 10.1504/IJOR.2016.073252

3. Ho W, Zheng T, Yildiz H, Talluri S. Supply chain risk management: A literature review. Int J Prod Res 2015;53(16):5031-69. doi: 10.1080/00207543.2015.1030467

4. Vanany I, Zailani S, Pujawan N. Supply chain risk management: Literature review and future research. International Journal of Information Systems and Supply Chain Management (IJISSCM) 2009;2(1):16-33. doi: 10.4018/jisscm.2009010102

5. Wisner JD, Tan K-C, Leong GK. Principles of supply chain management: A balanced approach: Cengage Learning; 2014.

6. Sarkis J, Schneider JL, Wilson A, Rosenbeck JM. Pharmaceutical companies and sustainability: An analysis of corporate reporting. Benchmarking: An International Journal 2010. doi: 10.1108/14635771011049371

7. Jaberidoost M, Nikfar S, Abdollahiasl A, Dinarvand R. Pharmaceutical supply chain risks: A systematic review. Daru 2013;21(1):69. doi: 10.1186/2008-2231-21-69

8. Rodriguez-Monguio R, Spielberger K, Seoane-Vazquez E. Examination of risk evaluation and mitigation strategies and drug safety in the us. Res Social Adm Pharm 2014;10(1):232-8. doi: 10.1016/j.sapharm.2013.03.005

9. Schommer JC, Pedersen CA, Worley MM, Brown LM, Hadsall RS, Ranelli PL, et al. Provision of risk management and risk assessment information: The role of the pharmacist. Res Social Adm Pharm 2006;2(4):458-78. doi: j.sapharm.2006.02.001

10. Ma Y. Risk management in biopharmaceutical supply chains: UC Berkeley; 2011.

11. Fawcett SE, Jones SL, Fawcett AM. Supply chain trust: The catalyst for collaborative innovation. Bus Horiz 2012;55(2):163-78. doi: 10.1016/j.bushor.2011.11.004

12. Park Y, Hong P, Roh JJ. Supply chain lessons from the catastrophic natural disaster in japan. Bus Horiz 2013;56(1):75-85. doi: 10.1016/j.bushor.2012.09.008

13. Akhondzadeh S. The economic aspects of medical biotechnology. Avicenna J Med Biotechnol 2016;8(1):1.

14. Afshari-Mofrad M, Salim A. Iranian firms in biopharmaceutical value chain: Where to go now? Journal of Science and Technology Policy Management 2019. doi: 10.1108/JSTPM-12-2018-0123

15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015 statement. Syst Rev 2015;4(1):1. doi: 10.1186/2046-4053-4-1

16. Beelmann A. Review of systematic reviews in the social sciences. A practical guide. 2006. doi: 10.1027/1016-9040.11.3.244

17. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (axis). BMJ open 2016;6(12):e011458. doi: 10.1136/bmjopen-2016-011458

18. Carlsson C, Fullér R, editors. On fuzzy screening systems. Proceedings of EUFIT'95 Conference; 1995.

19. Kuo Y-F, Chen P-C. Constructing performance appraisal indicators for mobility of the service industries using fuzzy delphi method. Expert Syst Appl 2008;35(4):1930-9. doi: 10.1016/j.eswa.2007.08.068

20. Chang K-F, Yang H-W. A study of cosmetic bundle by utilizing a fuzzy analytic hierarchy process (ahp) to determine preference of product attributers toward customer value. African Journal of Business Management 2011;5(22):8728. doi: 10.5897/AJBM10.933

21. Chen M-K, Wang S-C. The use of a hybrid fuzzy-delphi-ahp approach to develop global business intelligence for information service firms. Expert Syst Appl 2010;37(11):7394-407. doi: 10.1016/j.eswa.2010.04.033

22. Dehghani firouzabadi J, Beghiri A. Identifying the key factors of the civil war in the arab middle east using the fuzzy delphi method. Security horizons 2014;7(24):151-78.

23. Shah N. Pharmaceutical supply chains: Key issues and strategies for optimisation. Comput Chem Eng 2004;28(6-7):929-41. doi: 10.1016/j.compchemeng.2003.09.022

24. Leopoulos V, Kirytopoulos K, Voulgaridou D. Electronic alliances and the (para)pharmaceutical supply chain: Identification of risks. WSEAS Transactions on Systems 2006;5(1):279-84.

25. Breen L. A preliminary examination of risk in the pharmaceutical supply chain (psc) in the national health service (nhs)(uk). Journal of Service Science and Management 2008;1(2):193-9. doi: 10.4236/jssm.2008.12020

26. Enyinda C, Briggs C, Bachkar K, editors. Managing risk in pharmaceutical global supply chain outsourcing: Applying analytic hierarchy process model. ASBBS Annual Conference: LasVegas; 2009.

27. Blos M, Wee H-M, Yang J. Analysing the external supply chain risk driver competitiveness: A risk mitigation framework and business continuity plan. J Bus Contin Emer Plan 2010;4(4):368-74.

28. Enyinda CI, Mbah CH, Ogbuehi A. An empirical analysis of risk mitigation in the pharmaceutical industry supply chain: A developing-country perspective. Thunderbird International Business Review 2010;52(1):45-54. doi: 10.1002/tie.20309

29. Reschke CH, editor. Risk-identification and strategic foresight based on history, management and complex systems perspectives-the example of the bio-pharmaceutical industry. DRUID Summer Conference: Opening Up Innovation: Strategy, Organization and Technology; 2010: Imperial College London Business School.

30. Kaminsky P, Liu J, Olsen-Claire J. Survey: Optimizing global biopharmaceutical operations: Through risk mitigation and management. Biopharm Int 2012;25(12):38-43.

31. Jnandev Kamath K, Kamath K, Azaruddin M, Subrahmanyam E, Shabharaya A. Evaluation of different types of risks in pharmaceutical supply-chain. Am J Pharm Tech Res 2012;2:280-7.

32. Mehralian G, Gatari AR, Morakabati M, Vatanpour H. Developing a suitable model for supplier selection based on supply chain risks: An empirical study from iranian pharmaceutical companies. Iran J Pharm Res 2012;11(1):209-19. doi: 10.22037/IJPR.2012.1077

33. Ouabouch L, Amri M. Analysing supply chain risk factors: A probability-impact matrix applied to pharmaceutical industry. Journal of Logistics Management 2013;2(2):35-40. doi: 10.5923/j.logistics.20130202.01

34. Jaberidoost M, Olfat L, Hosseini A, Kebriaeezadeh A, Abdollahi M, Alaeddini M, et al. Pharmaceutical supply chain risk assessment in iran using analytic hierarchy process (ahp) and

simple additive weighting (saw) methods. J Pharm Policy Pract 2015;8(1):9. doi: 10.1186/s40545-015-0029-3

35. Vishwakarma V, Prakash C, Barua MK. A fuzzy-based multi criteria decision making approach for supply chain risk assessment in indian pharmaceutical industry. International Journal of Logistics Systems and Management 2016;25(2):245-65. doi: 10.1504/IJLSM.2016.078915

36. Huq F, Pawar KS, Rogers H. Supply chain configuration conundrum: How does the pharmaceutical industry mitigate disturbance factors? Production Planning & Control 2016;27(14):1206-20. doi: 10.1080/09537287.2016.1193911

37. Bucalo N, Jereb B. Risk management in the pharmaceutical industry in slovenian companies. Logistics & Sustainable Transport 2017;8(1):42-9. doi: 10.1515/jlst-2017-0004

38. Raka C, Liangrokapart J. An analytical hierarchy process (ahp) approach to risk analysis: A case study of a new generic drug development process. J Pharm Innov 2017;12(4):319-26. doi: 10.1007/s12247-017-9298-5

39. Enyinda CI. Modeling enterprise risk management in operations and supply chain: A pharmaceutical firm context. Operations and Supply Chain Management-an International Journal 2018;11(1):1-12. doi: 10.31387/oscm0300195

40. Moktadir MA, Ali SM, Mangla SK, Sharmy TA, Luthra S, Mishra N, et al. Decision modeling of risks in pharmaceutical supply chains. Industrial Management and Data Systems 2018;118(7):1388-412. doi: 10.1108/IMDS-10-2017-0465

41. Mahboudi F, Hamedifar H, Aghajani H. Medical biotechnology trends and achievements in iran. Avicenna J Med Biotechnol 2012;4(4):200.

42. Yousefi N, Ahmadi R, Tayeba H, Taheri S, Mahboudi F, Peiravian F. Biosimilar medicines in the iranian market: A way to more affordable medicines. Indian J Pharm Sci 2020;82(3):483-90. doi: 10.36468/pharmaceutical-sciences.671

43. Milanifar A, Akhondi MM, Paykarzadeh P, Larijani B. Assessing conflict of interest in iran's health legal system. Iranian Journal of Medical Ethics and History of Medicine 2011;5(1):1-16.

44. Kheirandish M, Rashidian A, Bigdeli M. A news media analysis of economic sanction effects on access to medicine in iran. J Res Pharm Pract 2015;4(4):199. doi: 10.4103/2279-042X.167042

45. Afshar Jahanshahi A, Al-Gamrh B, Gharleghi B. Sustainable development in iran post-sanction: Embracing green innovation by small and medium-sized enterprises. Sustainable Development 2019. doi: 10.1002/sd.2028

46. Fardazar FE, Asiabar AS, Safari H, Asgari M, Saber A, Azar AAEF. Policy analysis of iranian pharmaceutical sector; a qualitative study. Risk Manag Healthc Policy 2019;12:199. doi: 10.2147/RMHP.S209318

47. Marandi V, Tabatabaeian SH, Jafari P, Azarnoosh M. Policy coherence as a demand for excellence in iranian bio-production industry. Journal of Science and Technology Policy Management 2019. doi: 10.1108/JSTPM-12-2018-0111

48. Moradi M, Mirzadeh M. Identification, evaluation and ranking of manufacturing risks in the pharmaceutical industry using the fmea method (case study: Sobhan darou company). Journal of Healthcare Management 2019;10(1).

49. Zaboli P, Hashemi-Meshkini A, Varmaghani M, Gholami H, Vazirian I, Zekri H-S, et al. Pharmaceutical laws and regulations in iran: An overview. J Res Pharm Pract 2016;5(3):155. doi: 10.4103/2279-042X.185709

50. Ahmadi A, Milani A. Trade and ipr in iran: Trips issues and challenges. Global Trade and Customs Journal 2017;12(10):388-407.

51. Massoumi RL, Koduri S. Adverse effects of political sanctions on the health care system in iran. J Glob Health 2015;5(2). doi: 10.7189/jogh.05-020302

52. Boroumand S, Mohammadi T, Pajooyan J, Memarnejad A. The effect of exchange rate, oil prices and global inflation shocks on macroeconomic variables for the iranian economy in the form of a dsge model. Iranian Economic Review 2019;23(4):1057-83. doi: 10.22059/IER.2019.73003

53. Cheraghali AM. Impacts of international sanctions on iranian pharmaceutical market. Daru 2013;21(1):64. doi: 10.1186/2008-2231-21-64

54. Mytelka LK. Pathways and policies to (bio) pharmaceutical innovation systems in developing countries. Ind Innov 2006;13(4):415-35. doi: 10.1080/13662710601032770

55. Kaminsky P, Wang Y. Analytical models for biopharmaceutical operations and supply chain management: A survey of research literature. Pharm Bioprocess 2015;3(1):61-73. doi: 10.4155/pbp.14.57
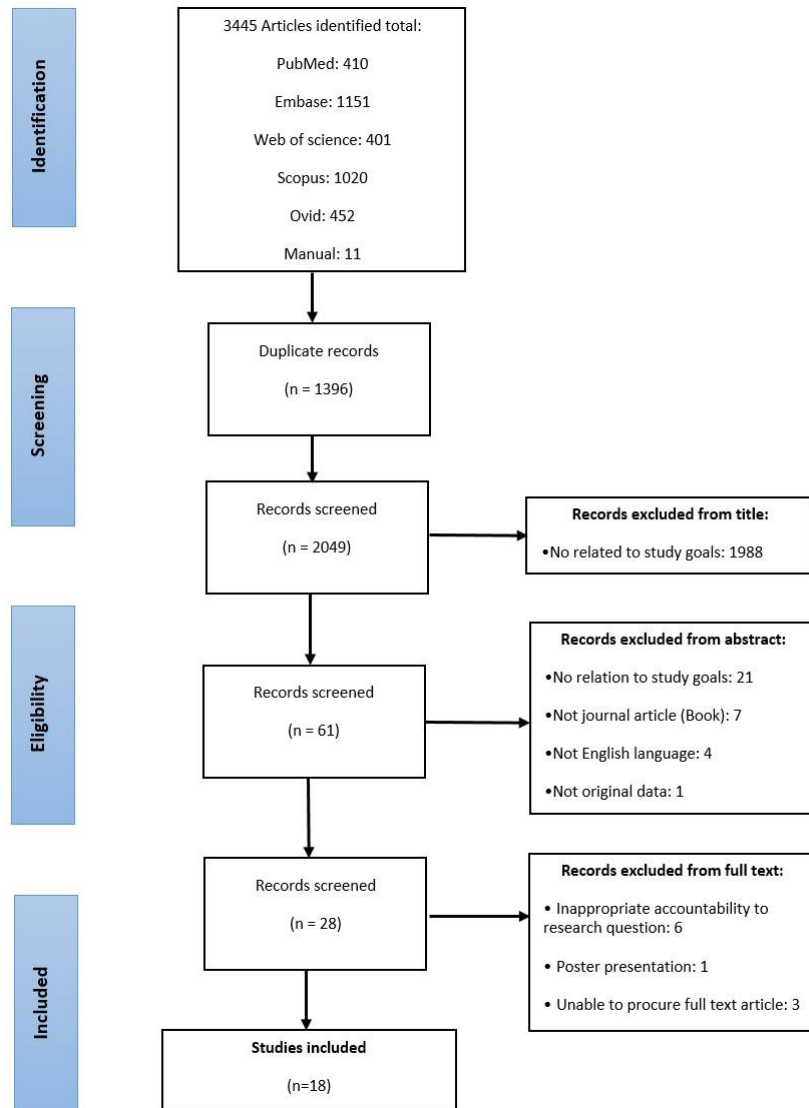
Figure 1. MOOSE flow diagram of observational studies included in the systematic review

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 limitations 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 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 & 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)

Category	risk	Selected (S)/ Rejected (R)	Category	risk	Selected (S)/ Rejected (R)
Financial factors	flexibility in product variety	1.64 (R)	Demand factors	contamination	2.93 (R)
	Inappropriate contract & agreements	4.07 (S)		Pseudo producity (mpacking product)	2.90 (R)
	long cash collection cycle	3.93 (S)		Marketing issues (International level)	2.58 (R)
	Inflexibility in delivering	1.59 (R)		Drug his	3.83 (S)
	Inflation rate	3.93 (S)		Demand fluctuations Restrictions	2.53 (R)
	Raw material price	3.40 (S)		Inappropriate Government policy distribution & coverage	3.27 (S)
	Bank exchange rate	1.74 (R)		Pricing policies	3.51 (S)
	Inflexibility in Quantities Cash flow	1.40 (R)		Inaccurate demand forecasting Biased	2.26 (R)
	Defect of Currency fluctuation	3.71 (S)		Interpretation of Regulations	3.47 (S)
	Interest rate	4.21 (S)		Product selection Customer services	2.18 (R)
	Business development issues	3.57 (S)		disruption Banking regulation	2.18 (R)
	Financial problems	3.57 (S)		Instability taste changes Lack of regulation	3.44 (S)
	New competitors	2.93 (R)			1.97 (R)
	Economic stagnation (new medicine or new company)	3.36 (S)			3.39 (S)
Logistic / Manufacturing factors	Target policies Single actor in the biopharmaceutical industry (exclusivity)	2.86 (R)	Regulatory factors / Management factors	MOH parafiky conflict of interest	4.15 (S)
		3.21 (S)		Sanctioning risks in the decision-making process	4.37 (S)
	changes	3.14 (S)		Political instability	3.40 (S)
	Return of investment	2.93 (R)		Lack of standard legislation & CROs for clinical policies trial	3.30 (R)
	Outsourcing related risk Capital fund management	2.93 (R)			3.39 (R)
	Motivation	2.43 (R)		Lack of efficient regulation structure for technology transfer Commercial regulation	2.96 (R)
	Tax payable change	2.43 (R)			2.30 (R)
	Counterfeit	2.18 (R)		Long-term licensing process for stablishing clinical trial	2.93 (R)
	Human errors	2.71 (R)			
	Transportation risks	1.85 (R)			
	Theft of goods	1.12 (R)			
	Time to market	2.71 (R)		Regulation & 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)

Appendix 1- database search strategy:

("risk management" OR "risk assessment") AND ("supply chain OR "production") AND ("pharmaceutical" OR "biomedicine" OR "biotechnology")

Search strategy	database	time	results
("risk management"[All Fields] OR "risk assessment"[All Fields]) AND ("supply chain"[All Fields] OR "production"[All Fields]) AND ("pharmaceutical"[All Fields] OR "biomedicine"[All Fields] OR "biotechnology"[All Fields])	PubMed	1 May 2019	410
((ALL=("risk management" OR "risk assessment")) AND (ALL=("supply chain" OR "production")) AND (ALL=("pharmaceutical" OR "biomedicine" OR "biotechnology"))) AND DOCUMENT TYPES: (Article)	Web of Science	1 May 2019	401
TITLE-ABS-KEY ("risk management" OR "risk assessment") AND TITLE-ABS-KEY ("supply chain" OR "production") AND TITLE-ABS-KEY ("*pharmaceutical" OR "biomedicine" OR "biotechnology")	Scopus	1 May 2019	1020
('risk management' OR 'risk assessment') AND ('supply chain' OR 'production') AND ('pharmaceutical' OR 'biomedicine' OR 'biotechnology')	Ovid Medline	1 May 2019	452
('risk management' OR 'risk assessment') AND ('supply chain' OR 'production') AND ('pharmaceutical' OR 'biomedicine' OR 'biotechnology')	Embase	1 May 2019	1151

Appendix 2: Semi-structured interview questions (translated into English)

Part 1.Introductory Questions

1. Please state how long have you been working in biopharmaceutical industry and how long have you been in your present job?

2. Please briefly describe your role in the company you are working at.

3. Please briefly explain the company's supply chain cycle.

4. Is the phrase "supply chain risk management" familiar for you? (Yes / No) Could you illustrate it in a few lines?

Part 2. Discussion of supply chain risk

5. Do you agree that nowadays Iranian biopharmaceutical companies are operating in a changing and uncertain environment? (Yes / No) Why?

6. Please, outline your understanding of the frequently occurring risks in biopharmaceutical supply chain. what are the main risks?

7. What are the sources of risk in a supply chain? Could you name them out? Do you consider them as external risks (suppliers, regulatory bodies) or you think they are internal risks.

8. Do you face various risks dealing with suppliers or customers from abroad?

9. Would you describe the risks in manufacturing, those that may not be mentioned in systematic review study results? Things like regulatory, financial, logistics, demand, macro factors, etc.

- The risks in regulatory:

- The risks in financial:

- The risks in logistics:

- The risks in demand:

- The risks in macro factors:

10. What are the main challenges in addressing the above issues?

To Close the Interview

11. Is there anything furthermore that you would like to be added to this study?