Implementation of Quality Risk Management by Application of HOR Method in Drug Development Process

Sweta Naresh Meshram
Second Year M. Tech Project Management,
Department of Manufacturing Engineering and Industrial Management
College of Engineering, Pune, Maharashtra, India
meshramsn20.mfg@coep.ac.in

Dr. Rajiv B.
Associate Professor, Department of Manufacturing Engineering
and Industrial Management
College of Engineering, Pune, Maharashtra, India
rbh.mfg@coep.ac.in

Abstract

As global healthcare has faced tremendous focus on the drug development process during the pandemic. During the pandemic, efforts were made to develop drug in couple of months, but every drug development process is bounded by risks. The drug development process tends to be lengthy and exhaustive process. Viewpoint of project management can assist in making the process rational with key milestones. Project risk management is one of the key areas of project, which focuses on quality and risk of project or process. This paper focuses on identifying and mitigating the risks encountered in the drug development process using the quality risk management framework and House of Risk (HOR) Analysis/Method. The study investigates the mitigation of the risks using the appropriate mitigation strategy. The House of Risk (HOR) model involves risk identification and risk mitigation. It enables to identify the risk at each step and mitigate them. The house of risk method ranks the risks and sets the appropriate priority for each of the risks encountered in the drug development process. After identifying the risk, the second phase of the house of risk method is to find the alternatives which can assist in mitigating the risks and consequently ranking them priority-wise. The results show that mitigation strategies determined in the study will enhance the drug development process.

Keywords
Quality risk management, drug development process, house of risk, analysis, risk identification and risk mitigation

1. Introduction
The drug development process is a complex process involving three key aspects – efficacy, quality and safety. The low success rate for clinical trials is due to any one of the key aspects or combination of them. Risks can arise at any stage of the drug development process and may become conducive environment for adverse risks to occur. The adverse risks may lead to discontinuation of drug development research program. The criticality involved in drug development process is high. Bacchieri A. et al. (2020) suggested from past research that, it is evident that the potential risks must be identified, and the corresponding mitigation plan should be established for the overall drug development process. From business standpoint, the cost involved is huge. The drug development process should justify the time and cost constraints to bring the drug to the market. The key principles of drug development process are optimizing trial cost, minimizing trial timeline and compliance with quality regulations. The drug development process tends to be lengthy and exhaustive process. Viewpoint of project management can assist in making the process rational with key milestones. Decision making plays a significant role in project management. Hallikasa. J et al. (2004) gave the idea that the forum of decision-makers are highly aware, by identifying the risks, about events that may bring uncertainties in the process.

Jorgensen. and Asgard. (2019) showcased the idea of developing and maintaining trust among the project team members. Moreover, if all the stakeholders are informed and their opinions are taken into consideration with due respect when taking critical decisions the trust is built in the team. Decisions related to risk mitigation strategy need to be taken by considering all the factors and not being biased on single dominant factor. Every organization has their own risk tolerance and based on that it depends if the action will be taken to handle the risk or not. The paper proposes the House of Risk Analysis Method to make decisions of risk prioritization and risk mitigation along with quality risk management framework.

1.1 Objectives
The research work presented in this paper commensurate deploy project management efficiencies throughout the drug development process. The primary objective is to mitigate the risks encountered in the drug development process. The most important job a project manager can play is to identify the upcoming risks and apply a visionary mindset to avoid risks or to take actions depending on the impact of the risks. In pharmaceutical industry, patient safety is of utmost importance. Throughout the drug development process, the controls need to be in place. However, where controls are not taken precautionary care there the patient is put at risk. Therefore, the recognition/ identification of risk is significant as it assists in figuring out the mitigation strategies which in turn allows to benchmark appropriate and mandatory controls, thereby safeguarding the life of many patients. The communication of risks amongst all stakeholders is critical in identifying and mitigating the risks. Therefore, communication of risks needs to be taken care of at every stage of the drug development process.

2. Literature Review
Quality risk management Q9 guideline given by ICH (2005) stated the framework for the assessing, controlling, communicating and reviewing risks to the across the drug development process. The assessment of the risk lies at the preliminary base of quality risk management and followed with applying control measures. Kumar and Jha (2018) suggested that quality risk management (QRM) is an activity that recognizing quality risks, assessing risk analysis, and finding mitigation strategies to overcome them. The initial step in quality risk management is identification of potential risks encountered in the drug development process. Talha et al. (2019) stated quality risk management process begins with the identification of unseen but forecasted risks. Identifying risk becomes easier with expert intervention in the process. Wayudin and Santoso (2016) mentioned in their research work that the biggest constraint in product development is tied to the emergence of uncertain risks, and it could be the major reason for failure of projects.

From project management viewpoint, it is very needed to keep awareness about all the risks which could occur. There are best practices to be kept in mind and one of the best practices is to list down all the risks which can be called as risk library. Suprin et al. (2019) recommended establishing the risk library to maintain the list of potential risks to enhance the risk identification process. Risk prioritization is the process is which all the risks are considered and consequently ranked priority-wise. The priority is given based on two criteria's – impact of the risk and probability of risk appearing. Identification and prioritization of risks is carried ultimately to control risks. The purpose of controlling risks is to find a risk mitigation strategy. Communicating the potential risks to all stakeholders is the primary responsibility of the project manager. Additionally, all the stakeholders are equally responsible to communicate the risks which can be foreseen. This approach will set a good example of team synergizing and working together to reduce the chances of risks threats and enhance the risk opportunities in the project. Aziz et al. (2018) stated in earlier research, risk communication includes sharing the information and feedback, internal and external to the project about risk activities, current risks and emerging risks. Jiang (2015) brought to notice that risk can dynamically impact the success of the project. Raveendran et al. (2022) suggested the concept of Dynamic Risk Analysis (DRA) in complex project management for continuous real-time method to deal with fast changing situations to track dynamic risks.

Since, the criticality of the drug development process is higher it is important to handle the risks encountered at each phase. Tanjung et al. (2019) stated that the value of risk can be determined by two basic criteria: possibility of risk (occurrence) and severity of risk (impact). The initial step of handling risk is identifying them at each stage of the process and mitigate them accordingly. Therefore, the aim of the study is to find critical risks and mitigate them in drug development process from project management perspective. The House of Risk (HOR) model is a framework involving risk identification and risk mitigation. It enables to identify the risk at each step and mitigate them.
The combination of quality risk management and house of risk method helps find the alternatives which can assist in mitigating the risks and consequently ranking them priority-wise. Raymond and Bergeron (2008) brought the concept

into light that in managerial tasks can be improved with maintaining good project plan involving scheduling, monitoring and control. The method is beneficial to the stakeholders involved in the entire drug development process owing to the time and cost involved.

3. Methodology

Aini et al. (2019) in previous research stated, for risk management of a project, HOR model proved as adynamic model for identifying and mitigating the risks. The study is conducted keeping in view the drug development process and the stages involved in it. In this paper, keeping project management perspective in focus, the plan is to identify and mitigate risks. The concept of quality risk management and house of risk analysis method is used to recognize and eliminate impact of the risks encountered in the drug development process. Wibowo and Ahyudanari. (2020) suggested that for the purpose of finding mitigation strategies, risk agents with maximum values of occurrence and impact are selected thereby reducing the risk agents with topmost priority.

The listings and ratings of risk agents and risk events are determined by interviewing the subject matter experts from drug development process. The risks are determined by considering the overall drug development process starting from discovery and development till the final stage of post marketing safety survey. The common ground is kept for rating the risk agents and risk events. The phase 1 matrix is for identifying the risks and in the phase 2 matrix, the mitigation strategies are listed and rated with the help of subject matter experts in the drug development process.

The steps involved in House of Risk Analysis Method for the drug development process are given below in chronological order –
1) The phase 1 of house of risk analysis method is identifying the risk events and the corresponding risk agents. Initially, determine the stages in drug development process
2) Determine the risk events and find the corresponding severity. Severity means the level of impact the risk will put on each stage of the drug development process. The standard scale of 1-10 is used (Table 1).

Table 1. Severity of risk events in the drug development process

Code	Risk Events	Severity
E1	Inefficiency in project management	8
E2	Safety of patients taking part in the clinical trial	9
E3	Selection of incompatible molecular composition	4
E4	New technology risk	5
E5	Side effects/ adverse events	7
E6	Glitches in study reports	7
E7	Communication risk (gulf of misunderstanding between stakeholders)	6
E8	All guidelines given by Food and Drug Application (FDA) are not considered	6
E9	Incomplete manufacturing information	2
E10	Tasks not completed on time	5
E11	Inefficient resource management	6
E12	Degradation of the quality of work	4
E13	Non-compliance/ protocol deviations	4
E14	Non-approval of drug application	3
E15	Prolonged delay in approval of the drug	3
E16	Delays in bringing the drug to the market	1
E17	Increased expenditure	5
E18	Increased attrition rate of patients (patients not appearing on the day of study)	5

3) Determine the risk agents and find the corresponding occurrences of the risks. Occurrence means the possibility of occurrence ofthe risk in the drug development process. The standard scale of 1-10 is used (Table 2).

Table 2. Occurrence of risk agents in the drug development process

Code	Risk Agents	Occurrence
A1	Human/ manual error	5
A2	Wrong process undertaken for disease identification	4
A3	Insufficient data sets and lack of information/ experience	5
A4	Mis-match of data in the clinical documents/ protocols	9
A5	Tests done inappropriately on patients (standard methodology not used)	2
A6	Wrong selection of molecular compounds	1
A7	Lack of experience in using technology	3
A8	Finalization of wrong frequency of dosages	2
A9	Wrong dosage calculations	3
A10	Wrong budget planning	8
A11	Written protocols not well-researched	4
A12	Not clarifying the guidelines (guidance documents) with approving institutions like FDA before proceeding with the clinical trial	4
A13	Lack of knowledge of manufacturing best practices	4
A14	Roles and responsibilities not clarified beforehand	5
A15	Missing timelines and majors milestones	6
A16	Complete information about the drug not provided	3
A17	Risk planning not considered during the drug development process	5
A18	Approval process is complex and involves lot of time	8
A19	Regulatory requirements and commitments have increased progressively over time	7
A20	Increase in both the trial size and the length	6
A21	Resources not utilized properly	6
A22	Risks not communicated to important stakeholders	7
A23	No regular tracking of the project plan of the drug development process	6
A24	Procurement of resources and service not efficiently handled	5
A25	Major risks unidentified	7

4) Determine the co-relation amongst risk event and risk agent in the drug development process. The scale of 9, 3, 1 and 0 is used. The scale of 9 states that the co-relation is strong, scale of 3 states that the co-relation is moderate, scale of 1 states that the co-relation is low and scale of 0 states that no co-relation exists amongst the risk event and the risk agent (Table 3).

5) Determine the aggregated risk of potential (ARP). It is calculated by using the following formula –

$$ARP_j = O_j \sum_j S_i \times R_{ij}$$

Table 3. Aggregated Risk of Potential (ARP) Calculation

Risk Event (Ei)	Risk Agent (Aj)																									Severity of risk event (Si)
	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17	A18	A19	A20	A21	A22	A23	A24	A25	
E1	3	3	3	3	3	1	3	1	1	9	3	9	3	9	9	3	9	3	3	3	9	9	9	9	9	8
E2	9	9	3	9	9	9	3	9	9	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	9	9
E3	9	0	9	9	9	9	9	9	9	0	3	3	0	0	0	3	0	0	0	0	9	0	3	0	9	4
E4	3	0	0	0	0	0	9	0	0	0	0	0	0	0	0	0	0	0	0	0	9	3	3	0	3	5
E5	3	9	3	3	3	9	3	9	9	0	9	9	3	3	0	9	9	3	3	3	9	3	3	0	9	7
E6	9	3	9	9	3	3	3	3	3	0	9	9	0	9	3	9	3	9	9	3	9	9	9	3	9	7
E7	0	0	0	0	0	0	0	0	0	0	0	9	0	9	9	3	9	3	3	3	9	9	3	3	9	6
E8	3	0	3	0	0	3	0	3	3	0	3	9	0	3	3	9	3	3	9	9	9	3	3	3	3	6
E9	3	0	0	3	0	0	0	0	0	0	0	0	9	0	0	0	9	0	0	0	0	0	0	3	3	2
E10	3	3	9	9	3	3	3	3	3	3	3	3	3	9	9	3	9	9	3	9	9	9	9	9	9	5
E11	3	3	3	3	3	3	3	0	3	9	3	9	3	9	3	3	3	3	3	3	9	3	9	9	3	6
E12	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	4
E13	3	3	3	3	3	3	3	9	9	0	9	9	0	0	0	9	3	3	3	3	3	3	3	3	9	4
E14	3	3	3	3	3	3	3	3	3	3	9	9	0	3	9	9	9	9	9	9	9	9	9	9	9	3
E15	3	3	3	3	3	3	3	3	3	3	9	9	0	3	9	9	9	9	9	9	9	9	9	9	9	3
E16	3	3	3	3	3	3	3	3	3	3	9	9	0	3	9	9	9	9	9	9	9	9	9	9	9	1
E17	3	3	3	3	3	3	3	3	3	9	3	3	3	3	3	3	9	3	3	3	3	3	3	3	3	5
E18	3	3	3	3	9	3	3	3	3	3	3	3	3	3	9	3	9	3	3	3	9	3	3	9	3	5
Occurrence of Agent (Oj)	5	4	5	9	2	1	3	2	3	8	4	4	4	5	6	3	5	8	7	6	6	7	6	5	7	
Aggregated Risk of Potential (ARPj)	1980	1284	1755	3537	690	359	918	730	1149	2280	1620	2316	756	2205	2484	1377	2685	3000	2667	2214	4104	3318	2916	2160	4452	
Priority rank	15	19	16	3	24	25	21	23	20	11	17	10	22	13	9	18	7	5	8	12	2	4	6	14	1	

6) The next step after identifying aggregated risk of potential ARP, is constructing the phase 2 of house of risk analysis method. The phase 2 matrix in the house of risk analysis method is for mitigating the risks. In this phase, initially determine and select the risk agents with the maximum ARP using the Pareto Analysis. From the Pareto analysis, the top three risk agents namely – A25, A21 and A4 are selected.
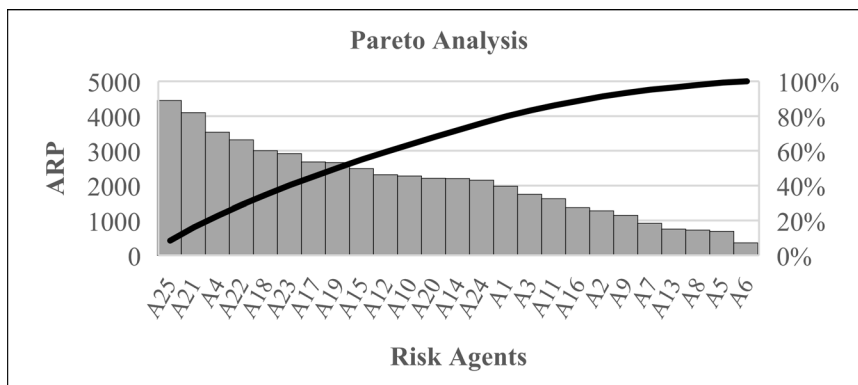

Figure 1. Pareto Analysis

7) The phase 2 matrix is determined by listing down the mitigation strategies with respect to the selected risk agents (Figure 1). The mitigation strategies are listed and the co-relation between risk agents and mitigation strategies are rated by again interviewing the subject matter experts involved in the drug development process by using a standard scale. The scale of 9, 3, 1 and 0 is used. The scale of 9 states that the co-relation is strong, scale of 3 states that the co-relation is moderate, scale of 1 states that the co-relation is low and scale of 0 states that no co-relation exists amongst the mitigation strategies and the risk agents (Table 4).

Table 4. List of Mitigation strategies

Code	Mitigation Strategy/ Preventive Action
MS1	Implementation of strategic resource and data management
MS2	Regular tracking of the project management plan
MS3	Building, implementing and tracking risk communication plan
MS4	Building, implementing and tracking project risk plan

8) In the phase 2 matrix, the total effectiveness of the mitigation strategy is calculated, and the formula used for determining total effectiveness is given below –

$$TE_k = \sum_i ARP_j \times E_{jk}$$

TE refers to total effectiveness, ARP refers to aggregated risk of potential and E refers to co-relation between risk event and risk agent.

9) Subsequently, the degree of difficulty is calculated. The degree of difficulty is rated by interviewing, brain storming, and coming to common agreed upon conclusions by subject matter experts. The standard scale of 1-10 is used.

10) The effectiveness to difficulty ratio is determined based on the calculations. The formula for effectiveness to difficulty ratio is shown below –

$$ETD_k = \frac{TE_k}{D_k}$$

ETD refers to effectiveness to difficulty ratio, TE refers to total effectiveness and D refers to difficulty of implementing the mitigation strategy.

11) Finally, the priority level of mitigation strategies is determined by ranking the effectiveness to difficulty ratio.

The flow diagram showcasing the methodology adopted for the research work, the integration of quality risk management and house of risk analysis, is shown below. The diagram is the combination of quality risk management and house of risk analysis method (Figure 2).
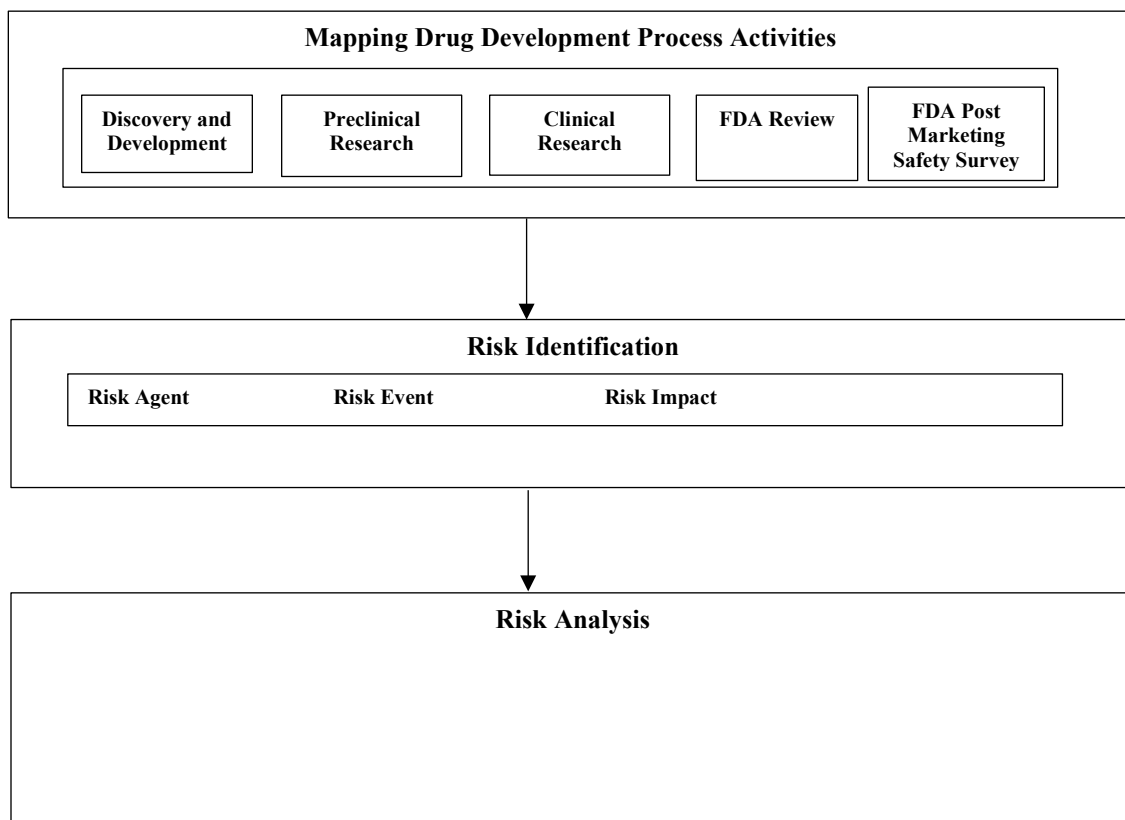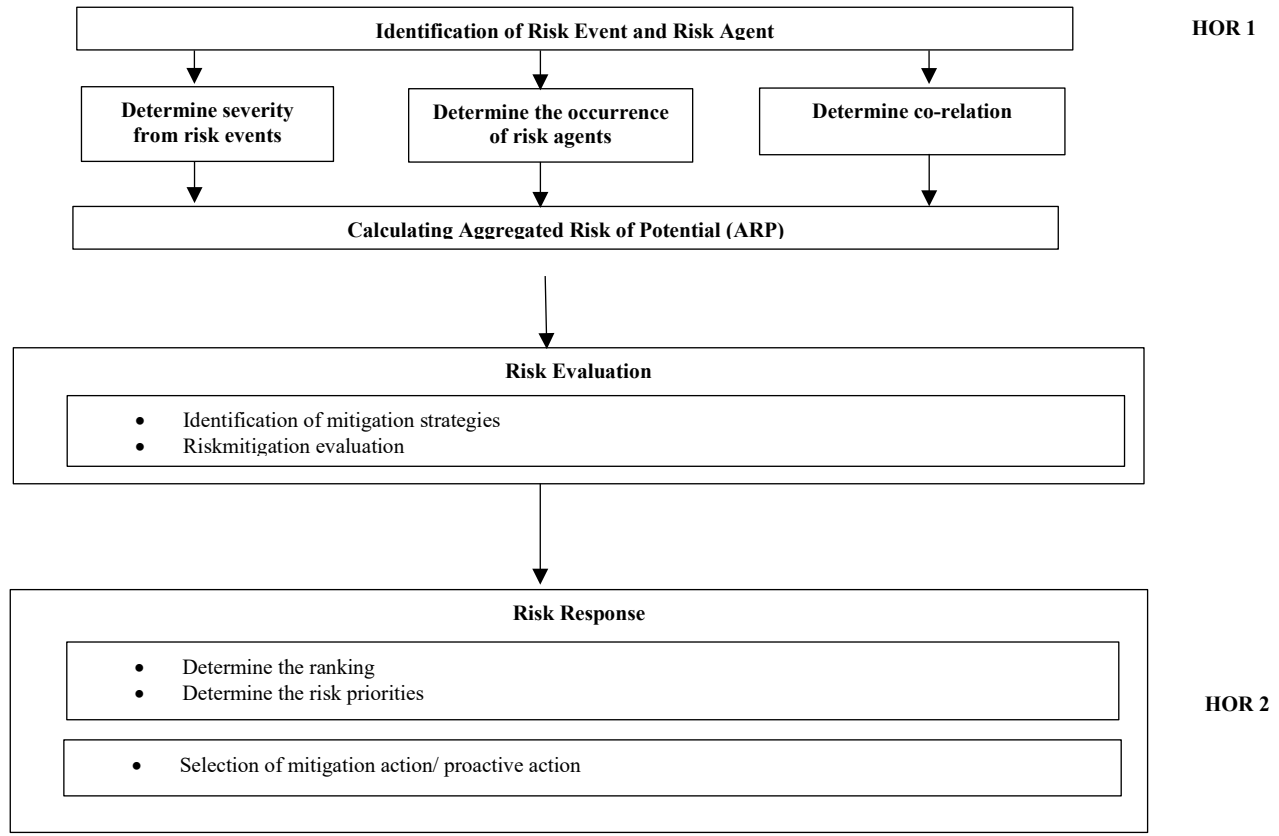
Figure 2. Flow diagram of the methodology

5. Results

According to the methodology, three topmost ranked risk agents are considered, and their mitigation strategies are listed priority-wise. The HOR –1 gives the Aggregated Risk of Potential (ARP) for all the risk agents. The risk agents A25, A21 and A4 are selected because they have the highest value of Aggregated Risk of Potential (ARP). The risk agent, A25 has the first highest value of ARP. Risk agent, A25, is of major risk unidentified. The mitigation strategy for A25 can be working on the project risk plan and communicating risks to the major stakeholders. The risk agent, A21 has the second highest value of ARP, is of resources not being utilized properly. The mitigation strategy for A21 can be optimally utilizing the resources. The risk agent, A4 has the third highest value of ARP, is of mis-match of data in the clinical documents/ protocols. The mitigation strategy for A4 can be strategically managing data (Table 5).

Table 5. Three topmost risk agents

Code	Risk Agent
A25	Major risks unidentified
A21	Resources not utilized properly
A4	Mis-match of data in the clinical documents/ protocols

HOR – 2 ranks the mitigation strategies. The risk agents A25, A21 and A4 are chosen are the highest ranked risk agents from HOR – 1. In HOR – 2, the mitigation strategies are listed on basis of the highest ranked risk agents – A25, A24 and A21. The ranking calculations of mitigation strategies are done thereby the ranks of mitigation strategies are obtained. The mitigation strategies are ranked in the order – MS1, MS3, MS4 and MS2 (Table 6).

Table 6. Ranking calculation of Mitigation strategies

Code	MS1	MS2	MS3	MS4	ARP
A25	3	9	9	9	4452
A21	9	3	3	3	4104
A4	9	3	9	3	3537
Total effectiveness	82125	62991	84213	62991	
Degree of difficulty	6	9	7	8	
Effectiveness to difficulty ratio	13687.5	6999	12030.43	7873.875	
Rank of priority	1	4	2	3	

Table 7. Raking of Mitigation strategies

Code	Mitigation Strategy/ Preventive Action	Rank
MS1	Implementation of strategic resource and data management	1
MS3	Building, implementing and tracking risk communication plan	2
MS4	Building, implementing and tracking project risk plan	3
MS2	Regular tracking of the project management plan	4

The results show that applying the basic project management efficiencies can help improve the overall drug development process (Table 7). Owing to the complex nature of the drug development process, it is highly encouraged to apply strong project management strategies and techniques to maintain smooth flow of the project within given timelines and cost. In addition, time and cost are greatly involved in the drug development process and hence, it is necessary to optimize the resources and mitigate risks strategically.

6. Conclusion

The research work presented shows, quality risk management gives impetus on risk communication which helps in mitigating risks before it leads to catastrophic failure in the drug development process additionally, smooth communication is the thin line which helps in risk mitigation in the drug development process. Therefore, it is essential to keep risk communication plan in the project to work more effectively and efficiently. Moreover, maintaining a project risk plan helps to keep awareness about all the upcoming good and bad risks in the project. Managing the resources optimally is equally important for success of the project. Managing data is critical for smooth functioning for the overall drug development process. To conclude, implementing the basic project management activities of tracking the project plan, optimization of resources, maintaining project risk plan, managing data and keeping the significant stakeholders informed about the risks helps enhance the overall drug development process and ultimately adds more years to the lives of patients.

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Biographies

Sweta N. Meshram is an engineering graduate completed her B.E in Electrical Engineering (Power and Electronics) from Nagpur Institute of Technology in 2017. Currently she is pursuing her Masters in MTech in Project Management specialization, Department of Manufacturing Engineering and Industrial Management from College of Engineering, Pune.

Dr. Rajiv B. is presently working as an Associate Professor in Department of Manufacturing Engineering and Industrial Management in College of Engineering, Pune. He has completed his Ph.D. in Production and Industrial Engineering and Master's in Production Engineering. His areas of expertise include Financial Planning and Management, Quantitative Techniques in Project Management, Manufacturing Engineering, Operations Research etc. He has guided 3 Ph.D. students and more than 85 ME/M Tech students. He had published over 90 papers in national and international journals and conferences. He has filed 4 patents and published 1 Textbooks in PHI New Delhi publication.