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**ROLE OF EFFECTIVE QUALITY RISK MANAGEMENT IN DRUG SAFETY PROJECT
MANAGEMENT**

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GRAD 699 PGMT

Table of Contents

Role of Effective Quality Risk management in Drug Safety Project Management	1
Abstract	3
keywords:	4
1. Introduction (2-4 pages).....	5
2. Problem Statement and Justification (1-3 pages).....	1
3. Literature Review -- Analysis of Related Work (4-5 pages).....	3
3. Methodology.....	7
4. Results	8
5. Discussion and Conclusion.....	2

ABSTRACT

Identifying risk is one of the key topics of discussion in project planning and update meetings. Project managers have to identify and manage different risks at various levels of projects. These risks must be managed and eradicated in effective and structured manner to perform effective quality risk management and thus leading to adequate project management. The research investigates the potential root cause of the quality risk management issues using tools such as fish-bone diagram (Ishikawa), 5-Whys, FTA etc. which could remedy this situation. An effectiveness check measure can also be implemented after applying corrective/preventive actions to ensure that quality is met at each step of the process. Over 90 articles were searched using key words risk minimization plan, benefit risk assessment, drug safety, and pharmacovigilance. The search was further narrowed to 16 articles which had information based on human studies and drug safety. Non-human studies and single case assessments were excluded from the research.

The quality data of 20 large pharmaceutical companies was surveyed extensively and it was suggested that only limited number of projects used very rare risk management practices and most of the projects do not use all the current tools of risk management. The most extensively used method of quality risk management included failure mode and effects analysis. This technique was mostly utilized in assessing change control and failed investigations. The data of this analysis suggested that risk management strategies are not used extensively. This research recommends practice of tools used for quality risk management such as fish-bone diagram (Ishikawa) and FTA at early stages of drug development. Effectiveness check measure is also suggested to ensure that quality is met at each step of the drug safety. There may be other risk

benefit assessment methods which are not identified by this research and further research is warranted to guarantee the success of these measures.

KEYWORDS:

Risk minimization plan, benefit risk assessment, drug safety, and pharmacovigilance

1. INTRODUCTION (2-4 PAGES)

Identifying risk is one of the key topics of discussion in project planning and update meetings. The project meetings usually assess the known risks and potential risks (which are predictable however, will require some more precision to uncover). Project managers have to identify and manage different risks at various levels of projects. These risks must be managed and eradicated in effective and structured manner to perform effective quality risk management and thus leading to adequate project management. Inadequate evaluation of risk impact assessment can further impact project objectives, scope, time, cost, and quality. It may also lead to incomplete identification of new uncertainties related to previously identified risks and may also lead to lack of transparency and miscommunications within and outside the team.

Despite tremendous efforts carried out by large pharmaceutical companies in quality risk management, and using risk management tools like fault-tree analysis (FTA), the misapplication of quality risk management is very common. Many pharmaceutical companies are more focused towards reacting to risks and correcting the risk rather than preventing them from occurring in initial stages of drug development process. The Companies take pride that they have most efficient risk management tools and quickly apply corrective and preventive actions (CAPA). However, with adequate application of risk management, these risks can be easily detected and prevented. The companies should focus more on preventive actions rather than being reactive. Even the formal risk management does not add value or precision to the situations because the root cause of the problems or risks are very superficially assessed which result in ineffective risk management. (J Vesper, 2016)

This problem has negatively affected both pharmaceutical companies and end users of the products i.e. patients enrolled in clinical trials of these pharmaceutical products. A possible cause of this problem is that the risk assessments usually only superficially address the root cause, which results in unsuccessful risk-control actions. Additionally, the risk management plans are frequently made by senior management who are busy and have hectic work schedule. These assessments are not very well supported by scientific rigor as they should be. Therefore, these assessments can be highly subjective and could lead to uncertainty in outputs further contributing to risks. (J Vesper, 2016)

If this problem is not solved then there is a risk that the pharma companies will lose their license to market the drugs. Thus, putting billions of dollars of these pharmaceutical companies at stake. Similarly, nonadherence to adequate formal risk management could risk the safety of patients enrolled in clinical trials thus increasing rate of mortality. Perhaps research that investigates the potential root cause of the quality risk management issues using tools such as fish-bone diagram (Ishikawa), 5-Whys, FTA etc. could remedy this situation. In the fish-bone diagram (Ishikawa) approach, the risks are stratified into multiple categories based on measurements, laboratory environment, human features, instrumentation, materials and methods. (Vogt, 2010, p. 797-812). While in FTA, the failure of the functioning of a process and product under study is assumed. In this tool, the failure of system is assessed via analysis of multiple of causes of risks. These multiple risks are combined to form a causal chain and results are presented in a pictorial presentation like tree of fault modes. Every level of this fault tree is designated with logical operators. This tool relies on understanding of subject matter experts to recognize causal factors (ICH Harmonised Tripartite Guideline, p.12). An effectiveness check measure can also be

implemented after applying corrective/preventive actions to ensure that quality is met at each step of the process.

2. PROBLEM STATEMENT AND JUSTIFICATION (1-3 PAGES)

Risks or uncertainties may sometimes jeopardize the capability of the project manager to achieve the planned objectives projects and may also impact scope, time and cost. This leads to failure of fulfilment of the project objectives and can lead to impaired planning, extension of project schedule and misunderstanding of responsibilities. (Project Management Institute). As a result of this likelihood of negative impact on a project's performance, the Project Management Institute recognizes risk management as one of the vital knowledge areas in the "Guide to the Project Management Body of Knowledge."

The problem statement for my research is:

1. How inadequate application of quality risk management plans impact effective project management in pharmaceuticals/drug safety projects.

The secondary questions which could arise from this research includes:

1. How technologies can be advanced to identify risks at initial stages of drug development.
2. How adequate planning in initial states of drug development can save the budget of the company and life of patients.

This problem has negatively affected both pharmaceutical companies and end users of the products i.e patients enrolled in clinical trials of these pharmaceutical products. If pharma companies don't solve it, there is a risk that the pharma companies will lose their license to market the drugs and this might also increase mortality rates of patients.

The research explores that the potential root cause of the quality risk management issues can be identified using tools such as fish-bone diagram (Ishikawa), 5-Whys and FTA in pharmaceutical companies. An effectiveness check measure can also be implemented after applying

corrective/preventive actions to ensure that quality is met at each step of the process. The primary literature search involved quantitative and qualitative methods used to assess benefit risk assessment. Internet based search engines were used to find relevant scientific publications and books. Secondary search included conference proceedings and regulatory internet websites.

Over 90 articles were searched using key words risk minimization plan, benefit risk assessment, drug safety, and pharmacovigilance. The search was further narrowed to 10 articles which had information based on human studies and drug safety. Non-human studies and single case assessments were excluded from the research. The research is restricted to review only published scientific risk benefit assessment techniques by using an internet based literature review of peer-reviewed journal articles. Many other risk–benefit methods based on unique clinical constraints were not included.

In addition to literature search, quality data for 20 large pharmaceutical companies was collected based on a standard matrix created for this analysis. The data of this analysis suggested that risk management strategies are not used extensively. Four of the 10 companies surveyed used risk assessment tools including fish-bone diagram (Ishikawa), 5-Whys and FTA. The most extensively used method of quality risk management included failure mode and effects analysis. This technique was mostly utilized in assessing change control and failed investigations. The research revealed that the risk management plans are frequently made by senior management who are busy and have hectic work schedule. These assessments are not very well supported by scientific rigor as they should be. The research suggests use of fish-bone diagram (Ishikawa), 5-Whys and FTA at the beginning of the projects so that majority of the risks can be eradicated at the initiation of the project. There may be other risk benefit assessment methods which are not

identified by this research and further research is warranted to guarantee the success of these measures.

3. LITERATURE REVIEW -- ANALYSIS OF RELATED WORK (4-5 PAGES)

As discussed, the key aspect of my research is to implement adequate risk management technologies for effective management of drug safety products. In today's time of increasing competition and globalization, project accomplishment has become even more analytical to measure the performance of business however, there are still some projects which suffer noncompliance, delays and failures. Currently pharma companies have well developed risk management tool however, still the success rates of projects is not as expected because either the project managers are unaware of use of risk management tools or these tools are misapplied in project planning and execution. (Tzvi Raz, 2002, p. 101-109).

In an empirical study devoted to analyzing use of risk management tools and techniques, the data of more than 100 projects completed in Israel in multiple industries were gathered. The level of use of risk management traditions were studied using probabilistic risk analysis, risk documentation, planning and trade-off analysis. In addition to this the variability of impact and application across various projects and their influence on numerous project achievement magnitudes was also studied. The data of this analysis suggested that risk management strategies are not used extensively. Of these 100 projects, only limited number of projects used very rare risk management practices and most of the projects do not use all the current tools of risk management. The projects using adequate risk management practices were found to be more successful therefore, these practices were related to the success of the project. (Tzvi Raz, 2002, p. 101-109)

The pharmaceutical industry currently employs wide variety of project management techniques and methodologies for few years, however, its overall development and influence are far behind when compared to other industries. (Byers, 1989, p. 11-12). Largely this is due to the intrinsic complications in managing the research and development projects. The newly developed technologies have inherent unpredictability which makes its necessary to work field of standard approaches to management of project. (Sheasley, 2016, p.37-43). Drug development is research oriented and highly risky endeavor. Market approval of one drug may take up to screening of 5000 compounds. Each compound may have its own inherent risk factors therefore, substantial resources gets exhausted in the early stages of development. Pharmaceutical companies end up spending around US\$350 to 500 million (including the cost of failed projects) for marketing of one drug. It is very common that drugs fail in prefinal stages of development i.e. phase III of clinical trials. The uncertainties at each step of drug development n necessitates the pharmaceutical companies to execute 40 to 50 projects so that the success of projects can be ensured and new chemical entities could be launched in market. Along with external risk factors there are inherent uncertainties at each step therefore, it becomes very difficult to be sure that the new drug will be as successful as desired or planned. The competitors in market may also launch comparators or comparable drugs during same time or unforeseen noxiousness may lead to withdrawal of drug from market. (Kaufman, 2002). An investigation results of a survey conducted for quality risk management of pharmaceutical and biopharmaceutical industries in 2015 and 2016 revealed that although substantial progress is made by pharmaceutical companies however, complete adoption of quality risk management techniques are not employed. These companies are nearly halfway in the direction of achieving complete maturity of quality risk management. (Waldron K, 2017, p.330-345)

Effective quality risk management strategies which investigate the potential root cause of the quality risk management issues using tools such as fish-bone diagram (Ishikawa), 5-Whys, FTA etc. will allow the companies to identify strengths, weaknesses, opportunities and threats of the projects. The adequate planning for uncertain events can make the companies ready for them whenever they arise. Using the above mentioned techniques can ensure success of the project and help the companies to define how potential risks can be identified. Once these potential risks are noted, the companies can design the risk management plan accordingly. Successful managers of projects always acknowledge that management of risk is vital, since accomplishing a project's objective and goals is dependent on preparation, execution, outcome and assessment which may lead to achievement of strategic objectives. Effective risk management approaches permit the companies to make the most of revenues and diminish the expenses on events which do not generate enough profit on investments. The detailed analysis of the risks may help project managers to plan and prioritize their work on the basis of the outcome of each step in the project. (Duggan, 2017)

Though health authorities frequently assess risks and benefits of any new drug during drug approval process, however, they do not typically complete quality risk benefit assessment nor is it accessible in a reliable and integrated framework when it is used. The presently used traditional process does not produce a clear, reliable, transparent, and cumulative quantification of the risks and lacks precision pertaining to the role of specific factors in the approvals. This does not permit the organized reassessment of risks over time. Therefore, the purpose of this literature review is to identify and describe the potential root cause of the quality risk management issues for pharmaceuticals industries. My research investigates that the potential root cause of the quality risk management issues using tools such as fish-bone diagram (Ishikawa), 5-Whys, FTA

etc. could remedy the situation of misapplication of quality risk management. An effectiveness check measure can also be implemented after applying corrective/preventive actions to ensure that quality is met at each step of the process.

3. METHODOLOGY

Based on the exhaustive literature evaluation, this research intentions at understanding the extent of acceptance, absorption and practice of the project risk management process, tools and techniques in the pharmaceutical segment. The general methodology of this analysis depends on a survey which was carried out to target the pharmaceutical industry and their management professionals internationally. The most important objective was to understand which tool among the ones available in risk management is used most frequently by majority of practitioners.

A controlled questionnaire methodology was implemented for this research as mentioned in the below sections.

Proposal of Questionnaire

The questionnaire was divided into three sections:

- Section 1 – Background Information- this explained if risk management is used in the industry
- Section 2 – Risk Management Processes-this explained what processes and standards are used by these companies
- Section 3 – Risk management Tools- this explained the tools used in risk management.

The distribution of the survey was done by using survey monkey. The link was sent to the recipients stating the objectives and scope of research. The survey was designed in order to entail suitable time for completion.

For the paper exclusively, the participation in Section 1 was prepared without inquiring the participants for personal details. Section 2 concentrated on gathering of participant responses regarding the risk management process. In this section, an evaluation of the existing tools and techniques used by participants was done. Section 3 - focused on professionals who use software tools for risk management in pharmaceutical industry.

The survey was available only in English language and was supposed to be answered online through a 48 hours accessible website without time limits for answering. Selection of an suitable and adequate

sample size of survey participant was done and 18 participants were selected. The survey participants majorly included physicians, doctors and executives in pharmaceutical industries.

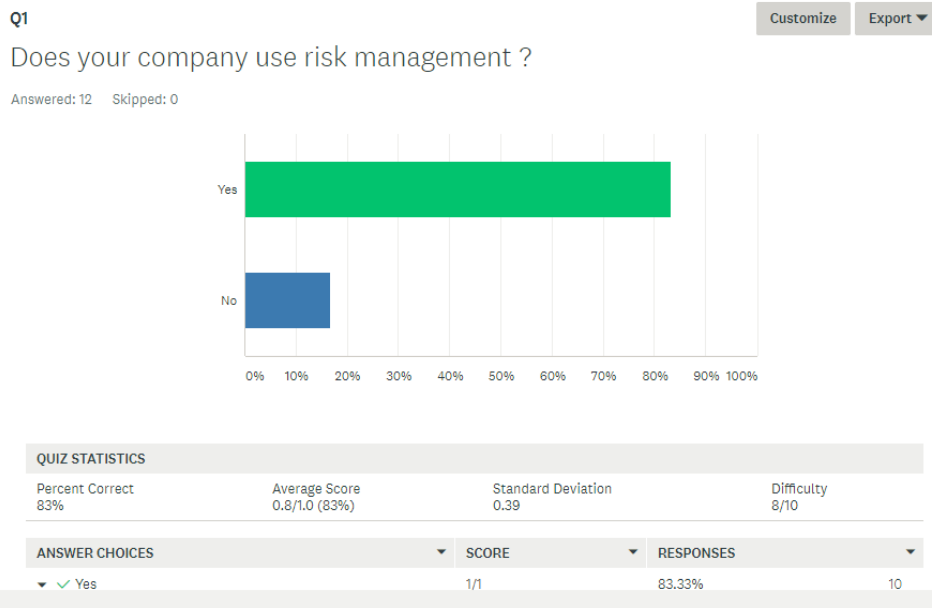
The questions of the survey were as follows: Risk management in pharmaceuticals companies

Industry: Pharmaceuticals

1. Does your company use risk management?
2. Does your company has any standards of risk management used eg; ISO
3. Do you have any system operational procedures that manage the risk identification, measurement, ranking, treatment, monitoring and recording?
4. Do you have a clearly defined organization structure to sustain risk management?
5. Do you evaluate risk when any important decision is made in the company?
6. Is there any training method used when a new process is implemented and how is this training documented?
7. Do you implement any inspection plan to reduce the inherent risks and do you revise it?
8. Do you use quality control checklists?
9. How frequently is Project Risk Response Audits performed
10. How frequently is brainstorming used

4. RESULTS

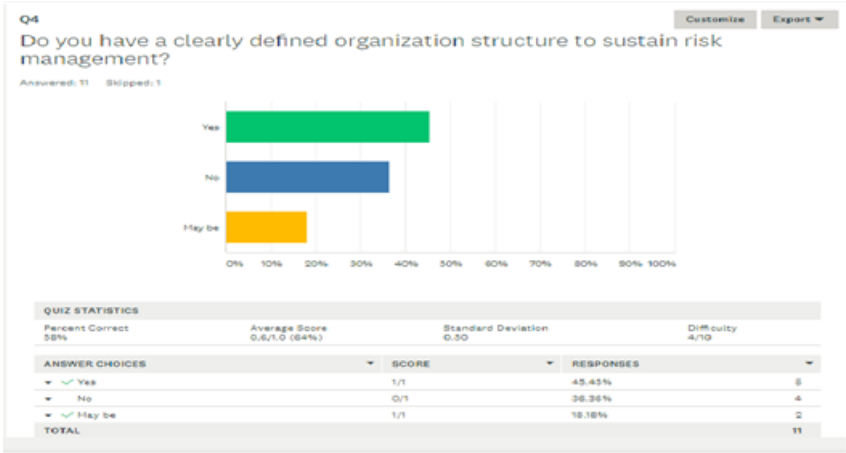
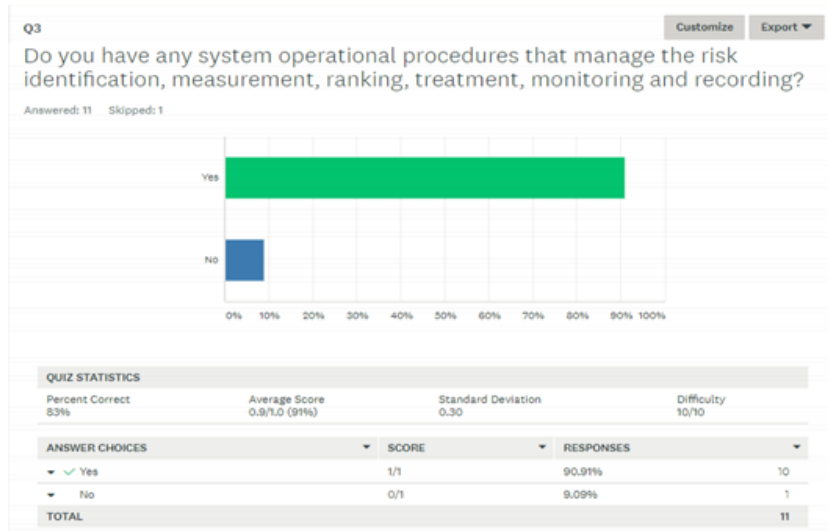
This segment displays the results of research; it establishes the investigation performed on composed data and the obtained results. The survey has been replied by a total of 12 respondents, from the United States and India. On comparison, more number of respondents were from USA. Survey results demonstrates that the standard risk management tools and techniques are majorly employed by pharmaceutical companies, along with some additional quality management tools. The overall survey results showed that 83% of the companies used risk management techniques in pharmaceutical drug safety projects.



However around 40% pharmaceutical companies do not follow nationwide accepted standards like ISO, lean six sigma etc. Every company had their own standards and procedures however, a globally accepted standard was missing in the companies.



Almost all the pharmaceutical companies consistently follow their standard operating procedures and have a well-organized structure to manage and sustain the risks.

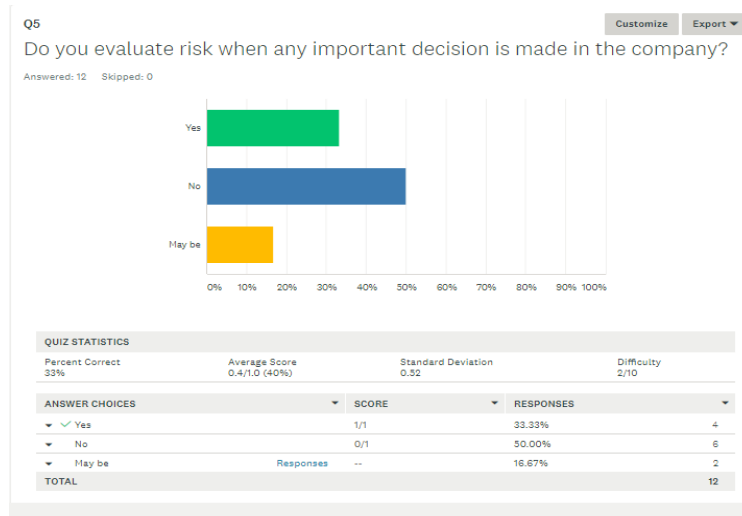


In general, the quality assurance team (QA) in these companies reviews the documented change request and carries out an impact assessment of the proposed change. During evaluation, the QA team:

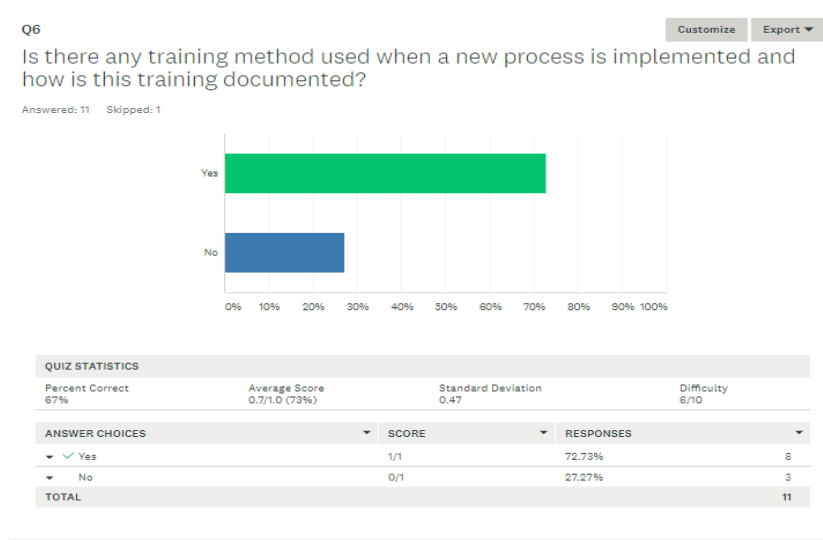
- Reviews the change details, reason for change and priority documented in the CRF by the initiator of change request.
- Assesses and documents the impact of the proposed change (whether critical, major or minor). The assessment should be all-inclusive and thorough to ensure that the consequences of implementing the proposed change are fully understood.

During evaluation, factors to be taken into consideration includes purpose, reasons, impact, cost, benefits and potential problems/risks. It also determined the level of management that needs to be informed of the 10

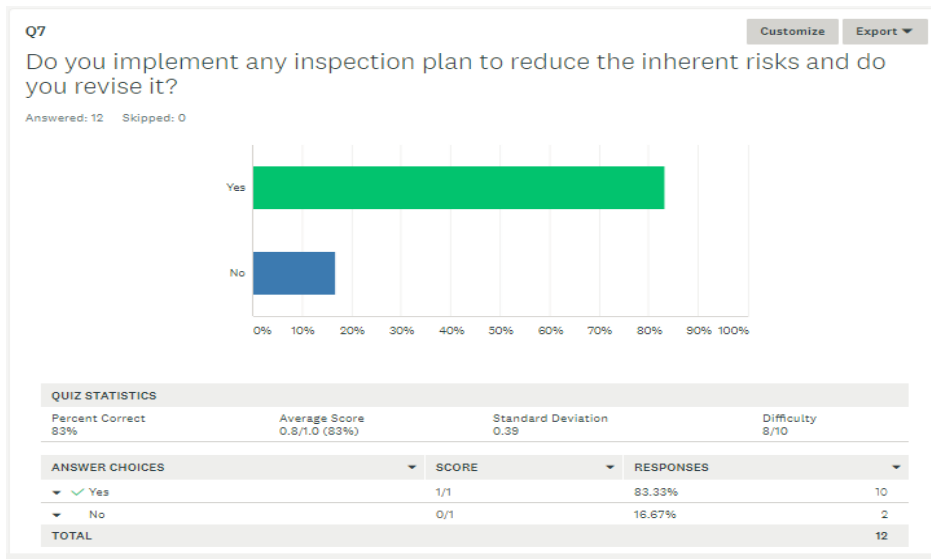
change and, additionally, obtain their approval. The approval authority reviewing the change request comprised of QA, senior management (Project Manager(PM)/Operations Head and/or the Corp. VP & GM, if required).



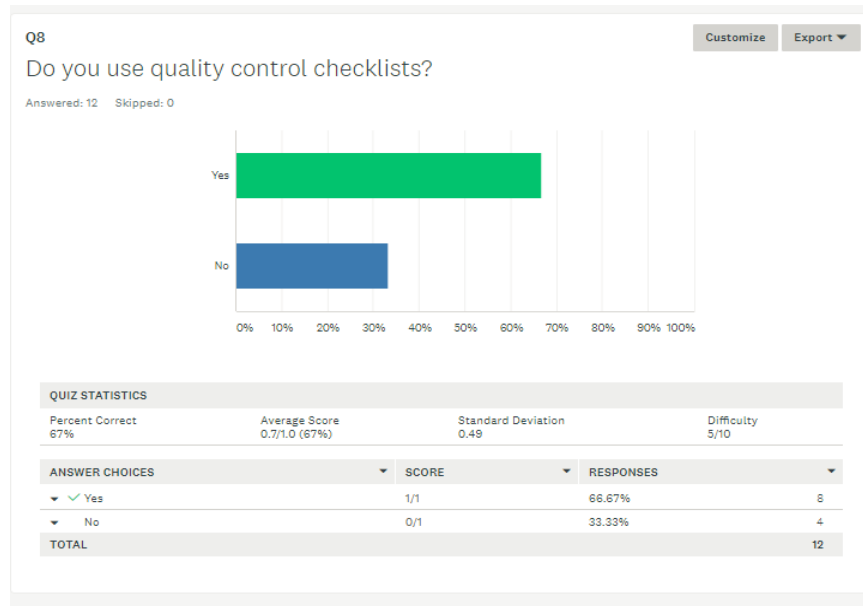
When looked at the survey results regarding decision making in the team, it was analysed that on average, 40% of the respondents use expert judgment rather than using any complicated quantitative Techniques. It was noted that most of the companies utilized convenient way of managing risks rather than using standard tools which are complex to handle.



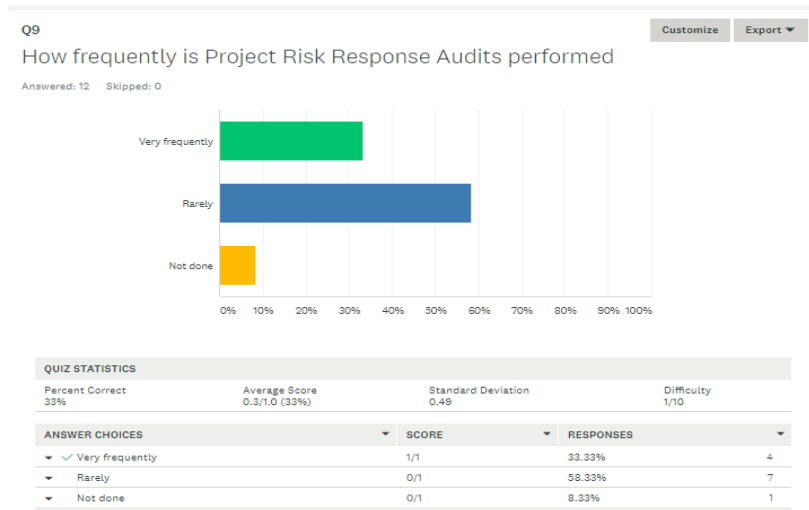
Most of the companies have a training and inspection plan organized for risk management in drug safety projects.



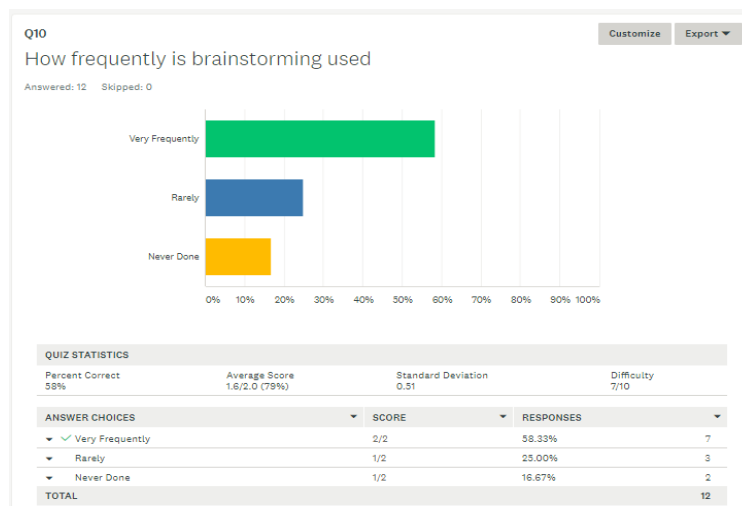
To our surprise the most frequently used to evaluate the quality in the drug safety projects was quality controlled checklists. Most of the companies had a formula operated checklists that was used to evaluate the quality of the work done during the projects.



The survey was also conducted to gather the responses on how frequently the companies perform internal audits. All the large pharmaceutical companies had a very high frequency of internal audits while some companies performed the audits on rare occasions.



As discussed earlier the companies looked for a more convenient way to handle risks rather than using complicated quantitative tools therefore, brainstorming was the most frequently used method for root cause analysis while managing the risks and corrective and preventive actions taken by companies.



5. DISCUSSION AND CONCLUSION

Based on the contribution of various pharmaceutical company's associates, doctors and nurse practitioners, the survey reveals the status of the project risk management practices, tools and techniques in the pharmaceutical industry for over 12 companies. The results show that majority of the pharmaceutical companies used convenient way to handle risks rather than using complicated quantitative tools therefore, brainstorming was the most frequently used method for root cause analysis while managing the risks and corrective and preventive actions taken by companies. It was further observed that the cost of the risk management is not very well optimized in these companies. The brainstorming method of analyzing the risk and the expert judgement do not necessarily help the professional to the fullest since these techniques may not be fully established and thus their functionality may not be as robust as anticipated.

Several benefit risk assessment techniques are available and could decrease the risks associated to drug safety. The research recommends practice of tools used for quality risk management such as fish-bone diagram (Ishikawa) and FTA at early stages of drug development. Effectiveness check measure is also suggested to ensure that quality is met at each step of the drug safety. There may be other risk benefit assessment methods which are not identified by this research and further research is warranted to guarantee the success of these measures.

The suggestions and guidance for future research in the area of project risk management practices can be that more tools of risk management would be introduced to the pharmaceutical market which are less complicated and have less inherent faults. It is suggested to the designers and manufacturers of risk management tools is to improve the efficiency of tools so that minimal amount of work is required to produce the desired results.

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