LITERATURE REVIEW:

Risk management is well known and practiced in many industries and several industry task forces have developed guidance documents that facilitate risk management. Risk management for the pharmaceutical has been documented in regulatory guidance.

1. Quality Risk Management guideline from the International Conference on Harmonization (ICH) provides an excellent high-level framework for the use of risk management in pharmaceutical product development and manufacturing quality decision-making applications. It is a landmark document in acknowledging risk management as a standard and acceptable quality system practice to facilitate good decision making with regard to risk identification, resource prioritization, and risk mitigation/elimination, as appropriate.¹ ²

2. Risk-based compliance was also a key component in the FDA's new approach for dealing with electronic records and signatures: 21 CFR Part 11.³

3. The World Health Organization Expert Committee on Specifications for Pharmaceutical Preparation published a paper entitled "Hazard and Risk Analysis in Pharmaceutical Products". It provides general guidance on the use of Hazard Analysis and Critical Control Points (HACCP) to ensure the quality of pharmaceuticals.⁴

4. The Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S) gave an example of a methodology for implementing ICH Q9 in the pharmaceutical field.⁵

5. In 2009 ISO released two more standards: ISO 31000 on "Risk Management Principles and Guidelines" and ISO 31010 on "Risk Assessment Techniques".⁶ Both standards are applicable to all industries.
6. The book gives an overview of the risk management process and some of the more commonly used risk assessment methods and tools. It also examines how the various tools can be applied to identifying hazards and evaluating their potential impact and effects.\(^7\)

7. Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach\(^{8-11}\) With this document the FDA introduced risk management to the pharmaceutical industry. In order to provide the most effective public health protection, the FDA must match its level of effort against the magnitude of risk. Resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production. Although the agency has already been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed.

8. Risk management is one of the focuses of this guidance. Risk-based approaches are expected to be used for setting specifications and process parameters, qualification of personnel, selection of quality unit (QU) personnel and for supplier auditing. Quality risk management is a valuable component of an effective quality systems framework. Quality risk management can, for example, help guide the setting of specifications and process parameters for drug manufacturing, assess and mitigate the risk of changing a process or specification and determine the extent of discrepancy investigations and corrective actions. The quality systems approach also calls for periodic auditing of suppliers based on risk assessment. As with other procedures, audit procedures should be developed and documented to ensure that the planned audit schedule takes into account the relative risks of the various quality system activities, the results of previous audits and corrective actions, and the need to audit the complete system\(^{10}\).

9. European Regulations, Annex 15 to the EU GMPs Validation and Qualification\(^{12}\) has legal status. It uses risk-based approaches to validation and for changes to facilities, systems and equipment. A risk assessment approach should be used to
determine the scope and extent of validation. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis.\textsuperscript{13-16}

10. Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S)\textsuperscript{16} was developed for inspectors but it is also a good source document for user firms. The inspector will consider the potential risks as identified and documented by the regulated user, in order to assess the fitness for purpose of the particular system(s).
Regulated users should be able to justify and defend their standards, protocols, acceptance criteria, procedures and records in the light of their own documented risk and complexity assessments, aimed at ensuring fitness for purpose and regulatory compliance.

11. An informal Working Group within PIC/S \textsuperscript{17} has developed an methodology for implementing ICH Q9 (29). The document is useful for training purposes and will not have an impact on PIC/S inspections.

12. United States Pharmacopeia (USP)\textsuperscript{18-19} develops methodology for specific applications and general chapters on different analytical aspects for FDA regulated industry. Most recently published final and draft chapters recommend risk benefit approaches for testing and using solvents.
\textless 232\textgreater  Elemental Impurities (Proposal). The presence of unexpected elemental contaminants, as well as that of impurities likely to be present, should be considered in determining compliance and planning the risk-based extent of testing.
\textless 467\textgreater  Residual Solvents. Solvents that are known to cause unacceptable toxicities should be avoided in the production of drug substances, excipients or drug products unless their use can be strongly justified in a risk benefit assessment.
13. ISO 14971:2007 - Application of Risk Management to Medical Devices was developed for medical devices but has also been recommended by FDA officials for pharmaceutical industry.

14. ISO 31000:2009 - Risk Management - Principles and Guidelines provides principles and generic guidelines on risk management. This International Standard can be applied throughout the life of an organization and to a wide range of activities, including strategies and decisions, operations, processes, functions, projects, products, services and assets. This International Standard can be applied to any type of risk, whatever its nature, whether having positive or negative consequences.

15. ISO 31010:2009 - Risk Assessment Techniques This International Standard is a supporting standard for ISO 31000 and provides guidance on selection and application of systematic techniques for risk assessment. Risk assessment carried out in accordance with this International Standard contributes to other risk management activities. The application of a range of techniques is introduced, with specific references to other International Standards, where the concept and application of techniques are described in greater detail.

16. The 3rd American Association of Pharmaceutical Scientists (AAPS)/Food and Drug Administration (FDA) Bioanalytical workshop in 2006 concluded with several new recommendations regarding the validation of bioanalytical methods in a report published in 2007. The purpose was to provide a “risk-based” reading of the recommendations of 3rd AAPS/FDA Bioanalytical Workshop.

17. Risk is dependent on expert judgement of the overall body of evidence relating to adverse effects or hazards. Such evidence can come from a range of experimental and observational studies and reports. Ideally determining risk to humans would be based upon evidence from humans rather than from
experimental animals but this is generally not feasible. Even when epidemiological studies are available there can be difficulties in ascribing a disease to a causal chemical agent, and there are inevitable limitations in assessing exposure.²⁴

18. This paper provides four case histories of risk management and post-marketing Surveillance programs utilized recently to address problems associated with possible abuse, dependence and diversion. The pharmaceutical sponsors of each of these drugs were invited to present their programs and followed a similar template for their summaries that are included in this article. They also illustrate the limitations of such programs in actually controlling unintended consequences, as well as the challenge of finding the right balance of reducing risks without posing undue barriers to patient access. These experiences are highly relevant as the FDA increasingly requires pharmaceutical sponsors to develop and implement the more formalized and enforceable versions of the risk management term Risk Evaluation and Mitigation Strategies (REMS).²⁵

19. The paper contributes to the academic discourse by empirically assessing differences in quality risk across domestic and offshore plants in a setting that naturally controls for many confounding factors.²⁶

20. Regulatory authorities evaluate the risks and benefits of any new drug therapy during the new drug-approval process, quantitative risk–benefit assessment (RBA) is not typically performed, nor is it presented in a consistent and integrated framework when it is used. In this paper published quantitative RBA methods for pharmaceuticals are identified and described. Several quantitative RBA methods are available that could be used to help lessen concern over subjective drug assessments and to help guide authorities toward more objective and transparent decision-making.²⁷
21. This article provides an overview of the recent adaptations brought to this original methodology taking advantage of our experience and the new regulatory framework, and, in particular, the risk management perspective introduced by ICH Q9. Although some alternate strategies have been introduced in our practices, the comparative testing one, based equivalence testing as statistical approach, remains the standard for assays lying on very critical quality attributes. This is conducted with the concern to control the most important consumer’s risk involved at two levels in analytical decisions in the frame of transfer studies: risk, for the receiving laboratory, to take poor release decisions with the analytical method and risk, for the sending laboratory, to accredit such a receiving laboratory on account of its insufficient performances with the method.28

22. The aim was to study of control limits for exposure to chemicals in air, food, water, and consumer products is to protect the whole human population, including the most susceptible individuals and ‘at risk’ groups. The existence of susceptible individuals is a factor that must be taken into account when quantitative chemical risk assessments are being made, and should be covered in the risk characterization.29

23. This paper discussed about the information that has been gained over the last three decades about the use of “short-term tests” for genotoxicity in cultured cells and in animals (mainly rodents), and the ongoing debates about the rational use of data from such experimental systems in trying to extrapolate to an understanding of potential human risk.30

24. The pharmaceutical industries are heavily regulated and the reasons are obvious: mistakes in product design or production can have severe, even fatal, consequences for patients which sometimes leads to recall of the drug from the market. Quality and its management are very critical in this industry. Total Quality Management (TQM) acts as an umbrella under which everyone in the organization can strive for customer satisfaction, reduce cost and wastage and
increase the efficiency of services. This paper surveys and reviews various Quality Management practices including ISO implementation in Indian pharmaceutical industries to explore the relationship between Total Quality Management practices and performance of the company.  

25. Teece’s complementary asset framework explains how firms use assets to appropriate the benefits of innovation. This paper extends Teece’s framework to show how firms also use complementary assets to inappropriate the risks of technical change. Based on case studies of the commercialisation of genetic testing in the UK the paper shows how firms can strategically alter the social distribution of risk to their advantage by managing distinct types of risk using different institutions with diverse risk management capabilities.  

26. There is a demand for pharmaceutical products with reduced abuse liability. These products must meet three tests to be successful. They must be safe for patients, be less likely to injure the abuser, and be less desirable for abuse by established drug abusers relative to existing products on a dose for dose (milligram-equivalent) basis.  

27. Increasing product/service complexity, outsourcing and globalisation have led to increasingly complex, dynamic supply networks. This has impacted on risk, changing it and changing its location in supply networks. This paper provides a review of definitions and classifications of types of risk; an holistic view of risk assessment and management is taken here. Little evidence is apparent of empirical research on risk in supply networks or tools to help identify, assess and manage that risk. A tool is provided and its testing and development in four case studies in the electronics sector is described.  

28. In order to ensure that risk assessment and risk management serve their purposes efficiently, it is essential to systematically evaluate actual practices. In this overview, it is proposed that such evaluation studies constitute an important
field of study that should be recognized as a sub discipline of regulatory toxicology with its own research issues and its own methodologies. Previous such evaluation studies are summarized. Methods are described that can be used for comparing different risk assessments of one of the same substance, for checking the consistency of harmonized classifications with the available data, for assessing the actual margin of safety (i.e. size of uncertainty factors) in exposure limits, and for comparing different lists of exposure limits.  

29. Failure Mode and Effect Analysis (FMEA) has been applied for the risk assessment of snails manufacturing. A tentative approach of FMEA application to the snails industry was attempted in conjunction with ISO 22000. Preliminary Hazard Analysis was used to analyze and predict the occurring failure modes in a food chain system (snails processing plant), based on the functions, characteristics, and/or interactions of the ingredients or the processes, upon which the system depends. Critical Control points have been identified and implemented in the cause and effect diagram (also known as Ishikawa, tree diagram, and fishbone diagram).

30. Failure mode and effect analysis (FMEA) is a powerful risk analysis tool that has been used for decades in mechanical and electrical industries. However, the adaptation of the FMEA methodology to biopharmaceutical processes brings about some difficulties. The proposal presented here is intended to serve as a brief but nevertheless comprehensive and detailed guideline on how to conduct a biopharmaceutical process FMEA. It includes a detailed 1-to-10-scale FMEA rating table for occurrence, severity, and detectability of failures that has been especially designed for typical biopharmaceutical processes.

31. Failure mode and effect analysis (FMEA) is a tool employed for clinical risk reduction. Employing FMEA, worked on a few critical activities, and reduced patients' clinical risk. A priority matrix also takes into account the weight of the
control measures: with FMEA this evaluation is quick, because of simple priority selection, and that it decreases action times.\textsuperscript{38}

32. The primary goal of post-marketing surveillance stated in the paper is to provide information for risk assessment of a drug. Drugs affecting the central nervous system form a unique group of products for surveillance because they are often misused, abused, and diverted. General risk management guidance has been developed by FDA, more specific analyses and guidance are needed to improve surveillance methodology for drugs which are misused, abused, diverted.\textsuperscript{39}