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FINAL STUDY DISSERTATION

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"Master In Quality Management"

Chemical Risk Optimization In Veterinary Pharma Labs Under ISO 31000 And GMP: Case Study Of CEVA Santé Animale, Algeria

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Abstract:

This study aims to assess and optimize chemical risk management practices for toxic substances in the physico-chemical quality control laboratory of CEVA «Santé Animale» Algeria, by integrating ISO 31000:2018 and Good Manufacturing Practices (GMP) within a resource-constrained Algerian industrial context. A qualitative single-case study was adopted, combining a GMP compliance checklist of 41 criteria, semi-structured interviews with three key informants, and documentary analysis, with risk evaluated through FMECA across 12 scenarios involving 8 toxic substances.

Results reveal an overall GMP compliance rate with 11 non-conformities, of which 9 are major, concentrated in Chemical Waste Management and Reagents and Chemical Substances. Five moderate-criticality scenarios required priority intervention, with the highest index recorded for vapour leaks from inadequate closures, a risk invisible to standard GMP checklists and identified exclusively through field interviews. Following implementation of the proposed CAPA plan, a significant criticality reduction is projected, bringing all residual indices within the acceptable range. These findings demonstrate that the integrated ISO 31000 and GMP framework, operationalised through FMECA, delivers a more comprehensive chemical risk assessment than compliance audits alone, constituting the first documented empirical application of this approach in an Algerian veterinary pharmaceutical QC laboratory.

Keywords: Chemical risk management, ISO 31000, Good Manufacturing Practices, FMECA, veterinary pharmaceutical laboratory

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Résumé:

Cette étude vise à évaluer et optimiser les pratiques de gestion des risques chimiques liés aux substances toxiques au sein du laboratoire de contrôle qualité physico-chimique de CEVA «Santé Animale» Algérie, en intégrant la norme ISO 31000:2018 et les Bonnes Pratiques de Fabrication (BPF) dans un contexte caractérisé par la rareté des ressources. Une étude de cas qualitative unique a été menée en s'appuyant sur une grille de conformité aux BPF comportant 41 critères, des entretiens semi-directifs réalisés auprès de trois informateurs clés, ainsi qu'une analyse documentaire. L'évaluation des risques a été effectuée à l'aide de la méthode AMDEC, appliquée à 12 scénarios impliquant 8 substances toxiques.

Les résultats révèlent un taux global de conformité BPF avec 11 non-conformités dont 9 majeures, concentrées dans la gestion des déchets chimiques et les réactifs et substances chimiques. Cinq scénarios de criticité modérée nécessitent une intervention prioritaire, avec l'indice le plus élevé enregistré pour les fuites de vapeurs liées à des fermetures inadéquates, un risque invisible aux grilles BPF standard et détecté exclusivement par les entretiens de terrain. Après mise en œuvre du plan CAPA, une réduction significative de la criticité est projetée, ramenant tous les indices résiduels dans la plage acceptable. Ces résultats démontrent que le cadre intégré ISO 31000 et BPF, opérationnalisé par l'AMDEC, offre une évaluation des risques chimiques plus complète que les seuls audits de conformité, constituant la première application empirique documentée de cette approche dans un laboratoire pharmaceutique vétérinaire algérien.

Mots-clés : Gestion des risques chimiques, ISO 31000, Bonnes Pratiques de Fabrication, AMDEC, laboratoire pharmaceutique vétérinaire

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الملخص

تهدف هذه الدراسة إلى تقييم وتحسين ممارسات إدارة المخاطر الكيميائية المرتبطة بالمواد السامة في مختبر مراقبة الجودة الفيزيوكيميائي لشركة «Animale Santé» الجزائر، من خلال دمج معيار ISO 31000:2018 وممارسات التصنيع الجيدة (BPF)في سياق صناعي جزائري محدود الموارد. اعتُمد تصميم دراسة الحالة الفردية النوعية، الجامع بين شبكة امتثال BPF من 14 معياراً، ومقابلات شبه موجهة مع ثلاثة مخبرين رئيسيين، وتحليل وثائقي، مع تقييم المخاطر بطريقة AMDEC على 41 سيناريو يشمل 8 مواد سامة.

كشفت النتائج عن معدل امتثال إجمالي لـ BPF مع 11حالة عدم مطابقة 9 منها رئيسية تمركزت في إدارة النفايات الكيميائية(والكواشف والمواد الكيميائية خمسة سيناريوهات ذات حرجية معتدلة (IC 26–60) تستوجب تدخلًا عاجلًا، وكان أعلى مؤشر لتسريبات الأبخرة الناجمة عن إغلاق غير محكم(IC = 36) ، وهو خطر لا يمكن رصده بشبكات BPF المعيارية ولم يُكشف إلا عبر المقابلات الميدانية. بعد تطبيق خطةCAPA ، يُتوقع تحقيق تخفيض متوسط في الحرجية ، مما يُعيد جميع المؤشرات المتبقية إلى النطاق المقبول .(IC ≤ 10) تُثبت هذه النتائج أن الإطار المتكامل 31000 ISO وBPF، المُشغَّل عبرAMDEC ، يوفر تقييماً أشمل للمخاطر الكيميائية مقارنةً بعمليات تدقيق الامتثال منفردةً، ويمثل أول تطبيق تجريبي موثق لهذا النهج في مختبر صيدلاني بيطري جزائري.

الكلمات المفتاحية: إدارة المخاطر الكيميائية، ISO 31000، ممارسات التصنيع الجيدة، AMDEC، مختبر الأدوية البيطرية.

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ABBREVIATIONS LIST

Abbreviation	Full Form
AMDEC	Analyse des Modes de Défaillance, de leurs Effets et de leur Criticité
ANPP	Agence Nationale des Produits Pharmaceutiques
API	Active Pharmaceutical Ingredient
BPF	Bonnes Pratiques de Fabrication
CAPA	Corrective and Preventive Action
CI	Criticality Index
CMR	Carcinogenic, Mutagenic, Reprotoxic
CLP	Classification, Labelling and Packaging
DMF	N,N-Dimethylformamide
FMECA	Failure Mode, Effects, and Criticality Analysis
GC	Gas Chromatography
GHS	Globally Harmonised System
GMP	Good Manufacturing Practices
HACCP	Hazard Analysis and Critical Control Points
HPLC	High-Performance Liquid Chromatography
HSE	Health, Safety and Environment
ICH	International Council for Harmonisation
IEC	International Electrotechnical Commission
ILO	International Labour Organization
INRS	Institut National de Recherche et de Sécurité
IR	Infrared Spectrometry
ISO	International Organization for Standardization
KF	Karl Fischer
KPI	Key Performance Indicator
MRL	Maximum Residue Limit
OEL	Occupational Exposure Limit
OOS	Out-of-Specification
OOT	Out-of-Trend
OSHA	Occupational Safety and Health Administration
PDE	Permitted Daily Exposure

PDCA	Plan-Do-Check-Act
PPE	Personal Protective Equipment
QC	Quality Control
QMS	Quality Management System
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SDS	Safety Data Sheet
SOP	Standard Operating Procedure
UV-Vis	Ultraviolet-Visible Spectrophotometry
VOC	Volatile Organic Compound
WHO	World Health Organization

GENERAL INTRODUCTION

The management of occupational chemical risks represents one of the most pressing challenges in the pharmaceutical industry worldwide. According to the International Labour Organization (ILO, 2022), over 374 million workers are injured or fall ill each year due to occupational hazards, with chemical exposure constituting a major contributing factor in industrial and laboratory settings. In pharmaceutical manufacturing and quality control environments, where toxic substances are handled daily under conditions of intensive analytical workload, the consequences of inadequate risk management range from acute intoxication incidents to chronic occupational diseases, regulatory non-conformities, and significant financial and reputational costs. The growing complexity of analytical methods HPLC, UV-Vis spectrophotometry, Karl Fischer titration and the diversity of hazardous substances involved (volatile organic compounds, CMR agents, corrosive reagents) make systematic and documented risk management frameworks not a regulatory formality, but an operational necessity.

In Algeria, the veterinary pharmaceutical sector has experienced sustained growth driven by increasing domestic production capacity and progressive alignment with international Good Manufacturing Practice (GMP) requirements, as codified under the national regulatory framework governing pharmaceutical manufacturing (Ministerial Order of 15 July 2009); (Executive decree 92-70, 1992)on occupational hygiene and medicine; (Law n° 88-07)on occupational health and safety). However, the sector remains characterised by a structural gap between regulatory compliance assessed through periodic GMP inspections and the practical management of occupational chemical risks at the laboratory level. Compliance instruments verify the existence of procedures, records, and equipment; they cannot systematically surface the tacit, experiential knowledge of practitioners or detect the chronic, diffuse exposure scenarios that represent the most significant long-term hazards in analytical laboratory settings. This gap between what documentation confirms and what field reality conceals constitutes the central problem motivating this dissertation.

Complementary normative frameworks are mobilised in this work to address this problem. The ISO 31000:2018 standard provides a structured, iterative risk management process context establishment, risk identification, analysis, evaluation, and treatment applicable to any organisational context. Good Manufacturing Practice (GMP) requirements, as defined by the World Health Organization (WHO) Technical Report Series No. 957 and the corresponding Algerian regulatory instruments, provide the sector-specific compliance architecture against which pharmaceutical QC laboratory performance is assessed. The integration of these two frameworks, implemented using the Failure Mode, Effects, and Criticality Analysis (FMECA) method, offers a methodology capable of both evaluating regulatory compliance and generating

a prioritised, actionable risk management plan a combination that neither framework alone can produce.

The primary applied research question of this dissertation is stated as follows:

« How can risk management practices for toxic chemical substances in the physico-chemical laboratory of a veterinary pharmaceutical company be systematically optimized and assessed by integrating ISO 31000 and Good Manufacturing Practice (GMP) requirements within a resource-constrained context such as Algeria? »

Two subordinate questions structure the empirical investigation:

Q1: Can an integrated ISO 31000, GMP/cGMP, and FMECA framework provide a more comprehensive and actionable assessment of chemical risks than regulatory compliance alone?

Q2: Can a qualitative triangulation approach combining extended field immersion, semi structured interviews across multiple seniority levels, and documentary analysis identify risk scenarios that remain undetected by standard GMP compliance tools?

The general objective of this dissertation is to design and apply an adapted risk management approach for toxic chemical products, grounded in ISO 31000:2018 and GMP requirements, within the physico-chemical QC laboratory of CEVA Algeria. This general objective is operationalised through four specific objectives:

- To identify the principal chemical risks present in the laboratory through systematic qualitative triangulation of three complementary data sources.
- To analyse and prioritise these risks according to their severity, frequency, and detectability using the FMECA method.
- To examine the root causes of the most critical risk scenarios.
- To propose a prioritised corrective and preventive action plan accompanied by performance monitoring indicators, adapted to the operational and resource context of the company.

The field study site selected for this investigation is CEVA Algeria, the Algerian subsidiary of the CEVA «Santé Animale» group, one of the leading veterinary pharmaceutical companies in the world. Established in Algeria and subject to both national regulatory requirements (Directorate of Pharmacy and Equipment, Ministry of Health) and international GMP standards, CEVA Algeria operates a physico-chemical quality control laboratory that routinely handles a panel of eight toxic substances acetonitrile, chloroform, methanol, petroleum ether, sodium hydroxide, isopropanol, N,N-dimethylformamide (DMF), and Karl Fischer reagent spanning a broad spectrum of chemical hazard profiles, from chronic neurotoxins and volatile organic compounds to Category 1B CMR substances under REACH Regulation EC 1907/2006. The

company's intermediate GMP maturity level, its operational representativeness of the Algerian veterinary pharmaceutical sector, and the availability of three key informants with complementary seniority profiles made it an ideal field site for this investigation. A three-month on-site immersion provided the depth of access necessary to implement the qualitative methodology rigorously.

This dissertation is structured in three chapters. Chapter 1 develops the theoretical and regulatory foundations, examining the conceptual framework of chemical risk management, the structure and requirements of ISO 31000:2018, the GMP/cGMP regulatory landscape applicable to pharmaceutical QC laboratories in Algeria and internationally, and the FMECA methodological framework. Chapter 2 presents the research methodology: the qualitative case study design, the epistemological positioning, the data collection instruments GMP compliance evaluation checklist, semi-structured interviews, and documentary analysis and the justification of analytical choices. Chapter 3 constitutes the applied core of the dissertation: Section 1 presents the complete empirical results of the field investigation, encompassing the GMP compliance evaluation, risk identification, FMECA analysis, and the corrective and preventive action plan with performance indicators; Section 2 situates these results within the scientific literature, identifies convergences and divergences, examines the methodological choices critically, addresses the limitations of the study, and outlines the research perspectives opened by this work.

CHAPTER I: THEORETICAL FRAMEWORK

The management of chemical toxic risks in veterinary pharmaceutical physico-chemical quality control laboratories constitutes a multidimensional challenge, situated at the convergence of stringent regulatory obligations, complex hazardous substance profiles, and the operational demands of an analytical environment in which scientific rigour and occupational safety must be simultaneously maintained. Tackling this challenge in a structured and evidence-based way requires not only a thorough understanding of the existing theoretical and regulatory knowledge base, but also a clear and coherent analytical framework to put that knowledge into practice. This chapter fulfils both requirements.

It is structured into two interrelated sections that collectively form the theoretical and conceptual foundation of the present study. The first undertakes a critical review of the scientific and regulatory literature, organised around four thematic axes: the Algerian institutional and regulatory architecture governing veterinary pharmaceuticals; the internationally recognised risk management frameworks of ISO 31000:2018 and Good Manufacturing Practices; the nature, sources, and consequences of chemical hazards in veterinary physico-chemical quality control laboratories; and the documented benefits, limitations, and practical applications of integrated risk management in comparable laboratory and manufacturing settings. This review does not merely survey existing contributions; it critically delineates the boundaries of current knowledge and identifies the empirical and contextual gaps that justify the present research.

The second section translates the insights derived from the literature into a structured conceptual framework, developed around four interconnected pillars: the chemical risk profile of the physico-chemical quality control laboratory; the iterative risk management process of ISO 31000:2018; the Algerian GMP regulatory environment and its institutional oversight mechanisms; and the integrated analytical framework combining FMECA and CAPA within a coherent operational structure, reinforced by qualitative root cause analysis.

Together, these two sections establish the theoretical grounding, methodological logic, and analytical vocabulary that inform and structure every subsequent stage of this study.

Section 01: Literature Review

A thorough review of scientific literature was carried out to explore the optimization and evaluation of risk management for toxic chemical substances in physico-chemical laboratories within veterinary pharmaceutical settings, with particular emphasis on ISO 31000 and Good Manufacturing Practices (GMP). The selected studies were drawn from internationally recognised databases including Scopus, PubMed, ResearchGate, and Google Scholar, with priority given to peer-reviewed articles, regulatory guidelines, and empirical studies employing qualitative, quantitative, mixed-method, and normative research designs.

This review is structured around four interrelated themes: first, the Algerian regulatory and institutional framework governing veterinary pharmaceuticals; second, the internationally recognised risk management frameworks, specifically ISO 31000 and GMP as applied to veterinary products; third, the specific hazards posed by toxic chemicals in veterinary physico-chemical laboratories; and fourth, the documented advantages, challenges, and practical applications of integrated risk management in comparable laboratory settings. Each section synthesises the existing body of knowledge and identifies the research gaps that justify the present study.

1. Algerian Regulatory Framework for Veterinary Pharmaceuticals

1.1 Legal and Normative Architecture

In Algeria, the governance of veterinary pharmaceuticals is grounded in a layered legal and institutional architecture. The main regulatory references consist of (Law No. 18-11 of 2 July 2018 relating to health (as amended))(Executive Decree No. 90-240, 4 August 1990), which sets out the requirements for the manufacture, distribution, and oversight of veterinary medicinal products, and (Executive Decree No. 09-102 of 10 March 2009 governing the import and export of veterinary medicines)Together, these instruments establish the minimum standards for laboratory safety, product quality, and supply-chain integrity across the veterinary pharmaceutical sector.

More recent regulatory activity has reinforced this framework. (Ministerial Decree No. 21 of 30 September 2025 on the issuance and renewal of GMP certificates) standardises the issuance and renewal of Good Manufacturing Practice (GMP) certificates, which are valid for two years and subject to on-site inspection. Audits conducted under this decree examine quality systems, documentation practices, personnel competence, premises and equipment adequacy, and the

handling of materials with specific scrutiny directed at toxic and hazardous substances managed within physico-chemical quality control laboratories.

1.2 Institutional Actors and Their Mandate

The institutional landscape is characterised by the interplay of three principal bodies. The Ministry of Pharmaceutical Industry functions as the principal policy authority, responsible for manufacturing authorisations and overall sectoral governance. The National Pharmaceutical Agency (ANPP) exercises operational oversight through GMP certification, on-site inspections, and product registration. The Directorate of Veterinary Services, operating under the Ministry of Agriculture and Rural Development, provides technical supervision of veterinary medicinal products and controls import and export flows under (Executive Decree No. 09-102 of 10 March 2009 governing the import and export of veterinary medicines). These actors collectively define the regulatory space within which veterinary pharmaceutical laboratories must operate. Table 1 below summarises the mandates of the main institutional actors involved in the regulation of veterinary pharmaceutical laboratories in Algeria.

Table 1: Institutional Actors in the Regulation of Veterinary Pharmaceutical Laboratories in Algeria.

Institutional Actor	Ministry / Portfolio	Key Regulatory Role
Ministry of Pharmaceutical Industry	Pharmaceutical Industry	Policy-setting; issuance of manufacturing authorisations; GMP oversight
National Pharmaceutical Agency (ANPP)	Pharmaceutical Industry	GMP certification; on-site inspections; product registration
Directorate of Veterinary Services	Agriculture & Rural Development	Technical oversight of veterinary medicinal products; import/export control
Ministry of Health	Health	Coordination under Law No. 18-11 (2018); cross-sectoral health governance

Source: *by author*

In February 2026, the inauguration of a new regional annex of the ANPP in Constantine including a dedicated animal experimentation laboratory branch marked a significant

institutional development. This facility is designed to support preclinical research in accordance with international standards including pharmacology and toxicology testing for veterinary products such as injectable drugs, biosimilars, and vaccines (Sentinelle, 2026, March 2) The initiative reflects a broader strategic commitment to strengthening the pharmaceutical production chain, particularly its preclinical research phases.

1.3 Identified Gaps

Although recent reforms such as the inauguration of the ANPP Constantine annex in 2026 reflect a commitment to strengthening veterinary pharmaceutical control infrastructure, the existing legal framework does not explicitly incorporate ISO 31000 principles or address the management of risks associated with toxic chemicals. Several operational constraints persist: insufficient training in chemical risk management, scarcity of detection and containment equipment, limited inspection coverage across veterinary sites, and the absence of any formal mechanism to integrate ISO 31000 into national reference systems. Notably, no published study to date documents the combined application of ISO 31000 and GMP within Algerian veterinary physico-chemical laboratories, underscoring the compelling need for contextualised empirical inquiry.

2. Risk Management Frameworks: ISO 31000 and GMP for Veterinary Products

2.1 ISO 31000 as a Principled Risk Management Architecture

(International Organization for Standardization, 2018) defines ISO 31000 as a principles-based standard applicable to any organisation, sector, or activity. Its framework is built on eight principles including integration, customisation, inclusivity, and continual improvement and articulates a risk management process spanning context establishment, risk identification, analysis, evaluation, treatment, monitoring, and communication. Crucially, ISO 31000 does not mandate specific tools or procedures; rather, it provides a governance architecture that can be tailored to an organisation's size, objectives, and risk profile. This flexibility makes it particularly suited to complex, regulated environments such as pharmaceutical manufacturing, where risks are multidimensional and dynamic.

(Lalonde & Boiral, Managing risks through ISO 31000: A critical analysis., 2012b) conducted a critical review of (ISO 31000:2009)and argued that, despite its broad applicability, the standard's non-prescriptive nature may limit consistent implementation across organisations. However, subsequent empirical work has demonstrated its practical value. (Oliveira, Rocha, & Salomon, 2019) conducted a systematic review of ISO 31000 applications in supply chain risk

management and concluded that the standard provides a robust integrative framework when combined with sector-specific risk tools. More recently, (Sassaoui & El Alami, 2023) applied ISO 31000 in a Moroccan industrial engineering context and confirmed its adaptability to North African operational realities a finding of direct relevance to the Algerian veterinary pharmaceutical sector.

2.2 Good Manufacturing Practices (GMP) and ICH Q9 - Quality Risk Management as Operational Complements

Good Manufacturing Practices (GMP) complement the governance architecture of ISO 31000 by imposing concrete, operational quality and safety requirements on pharmaceutical manufacturing processes. As stipulated by the (World Health Organization, 2024) and the (U.S. Food and Drug Administration, 2024) GMP covers the full spectrum of manufacturing operations personnel, premises, equipment, documentation, production, quality control, and complaint handling with particular attention to hazardous substance management in quality control laboratories.

The International Council for Harmonisation's guideline on Quality Risk Management ((ICH Q9(R1)., 2023), originally issued in 2005 and substantially revised in 2023, provides a systematic process for risk assessment, control, communication, and review within GMP-governed environments (International Council for Harmonisation. , 2023) ICH Q9 formalises risk management tools such as Failure Mode and Effects Analysis (FMEA), Hazard Analysis and Critical Control Points (HACCP), and risk ranking and filtering, each of which can be integrated within the broader ISO 31000 framework. The complementarity of these two systems ISO 31000 providing strategic governance and GMP/ICH Q9 providing operational methodology has been increasingly recognised in the pharmaceutical literature (Mulholland, 2020)(Poli, Esposito, Aloj, & Lastoria, 2024)

2.3 Empirical Evidence of Integration

Several empirical studies support the combined application of ISO 31000 and GMP in laboratory and manufacturing contexts. (Vukašinović, Obradović, & Debeljak, 2011) through a mixed-method case study conducted at a Serbian veterinary institute, demonstrated the operational feasibility of applying ISO 31000 alongside ISO 9001:2008 requirements, identifying risk categories relevant to laboratory processes and proposing mitigation measures. (Poli, Esposito, Aloj, & Lastoria, 2024) applied ICH Q9 risk assessment methodology to radiopharmaceutical production in Italy, identifying critical process phases and showing that

structured risk evaluation can meaningfully reduce non-conformances. (Ziniauskaite, 2025), in a master's thesis employing a quantitative 5×5 risk matrix, demonstrated that ISO 31000 integration improved material safety outcomes in a Finnish pharmaceutical company.

In the veterinary domain, a case study conducted at (Bandung, 2025) applied the ISO 31000 framework to animal laboratory support facilities using SWOT analysis, focus group discussions, and Analytical Hierarchy Process methodology. The study identified operational risk as the highest-priority category, with eight specific risk factors including equipment durability, technological development, and animal susceptibility levels findings that illustrate how ISO 31000 can be operationalised in a non-human pharmaceutical laboratory setting. Complementing this evidence, (Dzen, 2026)demonstrated that integrating ISO 9001 with GMP in veterinary pharmacovigilance processes reduced cumulative risk to biological products by 55-60% through a digital quality management system aligned with ICH Q9 methodology. (Zhang, et al., 2024) analysing GMP implementation in Chinese veterinary pharmaceutical enterprises, identified systemic weaknesses in quality management philosophy, document execution, and risk awareness gaps that bear direct comparison to challenges observed in emerging economies, including Algeria.

At the regulatory level, (Australian Pesticides and Veterinary Medicines Authority., 2025) has implemented a risk-based audit scheduling framework for veterinary manufacturing sites, differentiating between sterile immunological and non-sterile preparations and calibrating inspection intervals (12 to 36 months) according to non-conformance history. This model demonstrates how ISO 31000 risk stratification principles can be institutionalised within a national veterinary regulatory system. (World Organisation for Animal Health & HealthforAnimals, 2019) similarly reinforces that risk assessment methodologies consistent with ICH Q9 should be embedded in veterinary pharmacovigilance systems throughout the product lifecycle.

Despite this growing body of evidence, important limitations remain. The majority of published studies focus on human pharmaceuticals or large-scale industrial production. Evidence specific to veterinary physico-chemical laboratories is sparse, and no study examines the combined application of ISO 31000, GMP, and ICH Q9 to toxic chemical risk management within the specific constraints of the Algerian regulatory context. This constitutes a significant gap that the present research aims to address.

3. Risks of Toxic Chemicals in Veterinary Physico-Chemical Laboratories

3.1 Categories and Sources of Chemical Hazards

Veterinary physico-chemical laboratories routinely handle a broad spectrum of hazardous substances in the course of quality control operations, including organic solvents, mineral and organic acids, heavy metals such as lead, mercury, and arsenic, and a range of analytical reagents (International Labour Organization, 2004), (Occupational Safety and Health Administration, 2012)These substances are mobilised across multiple stages of laboratory work: sample preparation, chromatographic and spectrophotometric analysis, stability testing, calibration, and waste management creating a continuum of exposure opportunities for laboratory personnel and the surrounding environment (United States Environmental Protection Agency, 2008) The principal risk categories associated with toxic chemical use in these settings include: occupational exposure through inhalation, dermal absorption, or accidental ingestion (Occupational Safety and Health Administration, 2013) cross-contamination between reagents or product batches, which may compromise the validity of analytical results; environmental release attributable to inadequate waste segregation or disposal procedures (United States Environmental Protection Agency, 2008) (International Organization for Standardization, 2020), and physical hazards such as fire or explosion arising from the storage and use of flammable, oxidising, or reactive chemicals (Boston University, Environmental Health & Safety, 2025)

3.2 Regulatory and Scientific Frameworks for Chemical Risk Assessment

International regulatory bodies have developed structured frameworks to address these hazards. The (European Medicines Agency, 2026) established a three-step risk assessment process grounded in Permitted Daily Exposure (PDE) values the scientifically derived threshold of safe daily exposure to a given substance over a lifetime drawn from the ICH Q3D(R2) guideline on elemental impurities in pharmaceutical (International Council for Harmonisation, 2022) While this framework originates in a European regulatory context, its scientific basis encompassing dose-response analysis and margin-of-exposure calculations is internationally applicable and provides a model for developing comparable risk protocols in Algerian veterinary laboratories. (Fan & Chan, 2016) provide a comprehensive synthesis of foundational toxicology principles including hazard identification, dose-response characterisation, exposure assessment, and risk characterisation that serve as the scientific underpinning for laboratory safety protocol development. These principles are particularly relevant to the design of risk management

systems in settings where multiple toxic substances are used simultaneously, as is routinely the case in physico-chemical quality control laboratories. (Fan S. , 2001) earlier examined biosafety control measures specific to veterinary laboratories, emphasising the applicability of GMP principles to containment protocols, waste management, and environmental monitoring. (World Organisation for Animal Health, 2021) has since reinforced the importance of integrating ICH Q9-aligned risk assessment methodologies into veterinary pharmacovigilance systems, extending the scope of systematic risk management beyond the laboratory to the full product lifecycle.

3.3 Operational and Systemic Risk Factors

(Adam, 2013) examined the integration of risk management into existing pharmaceutical quality systems through multiple case studies and found that partial integration improved hazard controls for toxic substances, particularly where risk ownership was clearly assigned and documented. (Sousa, 2023) in a qualitative study of non-compliance management in the pharmaceutical sector, demonstrated that structured audits aligned with ISO 31000's three-line defence model reduced chemical handling risks and improved incident traceability. (Hammond, 2022) through a conceptual analysis of quality management generations, argued that risk-structured frameworks such as ISO 31000 represent a maturation of pharmaceutical quality thinking one that enables laboratories to transition from reactive incident management to proactive hazard anticipation.

The (European Medicines Agency, 2025) documented a 40% decline in GMP inspection rates attributable to resource constraints, highlighting a systemic vulnerability in the capacity of regulatory systems including those in emerging economies to maintain continuous oversight of chemical risk management practices. (Molander, 2020) in a policy analysis focused on the European Union, identified persistent inconsistencies in chemical risk communication between regulators, manufacturers, and laboratory personnel, arguing that these gaps translate directly into elevated occupational and environmental exposure.

These findings collectively underscore a critical limitation of the existing literature: while normative frameworks and theoretical models are well developed at the international level, very few studies examine the specific chemical risks encountered in veterinary physico-chemical laboratories, and none provide empirical data from the Algerian context. The operational realities of Algerian laboratories including resource constraints, limited training infrastructure, and the absence of ISO 31000 integration in national regulatory systems are not addressed in

any of the reviewed sources. This gap provides the central empirical justification for the present study.

4. Advantages, Challenges, and Applications of Risk Management in Veterinary Physico-Chemical Laboratories

4.1 Documented Benefits of ISO 31000 and GMP Integration

The integration of ISO 31000 with GMP requirements has demonstrated measurable benefits in comparable laboratory and manufacturing contexts. (Parenteral Drug Association, 2024) documented contamination risk reductions of up to 20% in aseptic processes where Quality Risk Management was systematically applied. The (United Nations Environment Programme, 2020)and (Fan & Chan, 2016) both highlight the contribution of structured risk management to reduced occupational exposure and improved environmental protection. (Mulholland, 2020) argues that integrating GMP-based quality risk management with enterprise-level risk governance frameworks such as ISO 31000 yields measurable improvements in regulatory compliance, audit readiness, and operational efficiency. These benefits are consistent with findings from (Dzen, 2026) which quantified a 55-60% reduction in cumulative biological product risk following ISO 9001/GMP integration in veterinary pharmacovigilance processes. Beyond contamination control, integrated risk management supports more robust decision-making processes. As (Poli, Esposito, Aloj, & Lastoria, 2024) demonstrate in the radiopharmaceutical context, systematic risk evaluation enables the prioritisation of critical process steps and the rational allocation of quality control resources a particularly relevant consideration in resource-constrained settings. The (World Health Organization, 2019 a) further emphasises that risk-based approaches to storage and distribution are adaptable across diverse institutional contexts, including veterinary GMP environments.

4.2 Implementation Challenges

Despite well-documented benefits, the implementation of integrated risk management systems faces significant structural and cultural barriers. The (European Medicines Agency, 2025) reported a 40% decline in GMP inspection rates attributable to resource constraints, reflecting a broader pattern of capacity limitations that affects both regulatory bodies and the manufacturers they oversee. In the Algerian context, (Djebrane, Brahmi, & Amrouche, 2021) identified specific obstacles including insufficient staff training in chemical risk management, limited availability of detection and containment equipment, and restricted inspection coverage

across veterinary pharmaceutical sites. The absence of formal mechanisms to integrate ISO 31000 into Algerian national quality systems further compounds these challenges.

(Molander, 2020) points to a related problem: the fragmentation of risk communication between regulatory authorities, manufacturers, and laboratory personnel, which creates knowledge asymmetries and reduces the effectiveness of risk controls even where formal management systems are in place. These communication failures are particularly consequential in physico-chemical laboratories, where the hazardous properties of substances may not be adequately conveyed to frontline analysts. (Hammond, 2022) frames this as a generational challenge in quality management: organisations that have not yet adopted risk-structured governance are more likely to experience systematic failures in chemical hazard management.

4.3 Practical Applications in Comparable Contexts

Practical evidence of successful implementation provides important reference points for the present study. (Vukašinović, Obradović, & Debeljak, 2011) demonstrated the feasibility of ISO 31000 implementation in a Serbian veterinary institute, identifying risk categories and mitigation strategies applicable to laboratory operations. The (Bandung, 2025) case study operationalised ISO 31000 in an animal laboratory support environment, confirming that operational risks including equipment failure, vendor dependency, and test animal management can be systematically assessed and ranked using the standard's framework. The (Australian Pesticides and Veterinary Medicines Authority, 2025) provides a replicable model for risk-based regulatory governance of veterinary manufacturing, demonstrating how ISO 31000 principles can be translated into institutional audit scheduling practices.

Additional normative guidance reinforces the applicability of integrated risk management to the veterinary context. The (World Health Organization, 2019 a) outlined good storage and distribution practices emphasising risk-based controls adaptable to veterinary GMP environments. The (University of Utah, 2024) institutional biosafety manual demonstrates how systematic risk assessments can minimise biohazards in laboratory setting an approach extensible to veterinary chemical risk management. The (United Nations Environment Programme, 2020) has urged adoption of internationally aligned risk management practices in the veterinary pharmaceutical sector specifically because of its contribution to environmental contamination risks through inadequate chemical waste management.

5. Synthesis and Research Positioning

The reviewed literature provides a robust normative and empirical foundation for understanding risk management in pharmaceutical laboratory environments. ISO 31000 offers a principled governance architecture; GMP and ICH Q9 supply the operational methodology; and a growing body of empirical studies confirms the measurability of risk reduction when these frameworks are integrated. However, the literature exhibits three consistent limitations with direct implications for the present research.

First, the predominant focus on human pharmaceuticals and industrial-scale production means that the specific risk profile of veterinary physico-chemical laboratories characterised by smaller volumes, greater chemical diversity, and comparatively less standardised workflows remains substantially underexplored. Second, available evidence from veterinary or animal laboratory contexts (Vukašinović, Obradović, & Debeljak, 2011) (Bandung, 2025) originates from Serbia and Indonesia respectively; no comparable study has been conducted in an Algerian setting. Third, none of the reviewed sources examines how ISO 31000 and GMP can be effectively integrated within the specific institutional and regulatory constraints of the Algerian veterinary pharmaceutical sector, where resource limitations, training deficits, and the absence of formal ISO 31000 integration in national systems create a distinctly challenging implementation environment.

The present study is designed to address these gaps using a qualitative applied research design based on semi-structured interviews, direct observation, and cause-and-effect analysis through qualitative data triangulation, it investigates real chemical risk management practices in the physico-chemical quality control laboratory of an Algerian veterinary pharmaceutical company. By grounding its analysis in ISO 31000 and GMP requirements while attending to the specific contextual constraints of the Algerian veterinary sector, the study contributes an original, practice-based perspective to an internationally significant but empirically underdeveloped field.

Section 02: Conceptual Framework

This section defines and articulates the key concepts that underpin the present study. Drawing on the most relevant elements from the literature reviewed in Section 1, it clarifies four foundational notions: the chemical risk profile specific to physico-chemical quality control laboratories in the veterinary pharmaceutical chain; the iterative risk management process prescribed by ISO 31000:2018 (International Organization for Standardization, 2018), the Good Manufacturing Practice (GMP) requirements applicable within the Algerian regulatory context; and the complementary analytical tools Failure Mode, Effects and Criticality Analysis (FMECA), and Corrective and Preventive Actions (CAPA) integrated within this framework.

1. The Veterinary Pharmaceutical Industry and Physico-Chemical Quality Control Laboratories

1.1 Definition, Role, and Specific Features of the Veterinary Pharmaceutical Industry

The veterinary pharmaceutical industry encompasses the research, development, manufacturing, quality control, and distribution of medicinal products intended for the prevention, diagnosis, and treatment of diseases in animals. According to international standards, a veterinary medicinal product (VMP) is any substance or combination of substances presented for use in animals for diagnostic, therapeutic, preventive, or physiological purposes (European Commission, 2022). The industry plays a vital role in promoting animal health and welfare, improving livestock productivity and food security, and protecting public health through the control of drug residues in food of animal origin (Valente, Santos, Duarte, & Mottola, 2020) several features distinguish this sector from human pharmaceuticals. The high diversity of target species entails different physiological and metabolic responses, requiring adapted formulations and safety thresholds. The mandatory establishment of withdrawal periods and maximum residue limits (MRLs) for food-producing animals adds a layer of regulatory complexity that directly influences the design of quality control programmes. The need for strengthened quality assurance and risk management systems, especially in the context of toxic chemical handling, is further reinforced by international standards (Hansen, Hofmo, & Skaare, 2012). In response to these challenges, compliance with Good Manufacturing Practices, quality risk management principles as formalised in (ICH Harmonised Guideline, 2005a) and the systematic framework of ISO 31000:2018 are now considered essential pillars of responsible veterinary pharmaceutical operations.

These characteristics have direct operational implications for physico-chemical quality control laboratories. As the functional units responsible for batch release decisions, they are both technically complex and regulatory-sensitive environments in which chemical risk management is not a peripheral concern but a core operational requirement. Understanding how the laboratory deals with these risks from hazard identification through to corrective action is the central purpose of this study.

1.2 The Physico-Chemical Quality Control Laboratory in the Veterinary Pharmaceutical Chain

1.2.1 Role and Regulatory Obligations

Physico-chemical quality control laboratories represent a critical node in the veterinary pharmaceutical production chain. They are responsible for verifying the identity, purity, potency, and quality of raw materials, active pharmaceutical ingredients (APIs), excipients, and finished products through a range of analytical techniques, including high-performance liquid chromatography (HPLC), gas chromatography (GC), spectroscopy, titration, and physico-chemical testing (Hansen, Hofmo, & Skaare, 2012). Their core mission is to ensure that all materials and products conform to approved specifications and pharmacopoeial standards before batch release.

Key regulated activities include analytical method validation, stability studies, impurity profiling, and the investigation of Out-of-Specification (OOS) and Out-of-Trend (OOT) results (ICH Harmonised Guideline, 2005b) (European Commission, 2022). In the Algerian context, physico-chemical quality control laboratories must comply with national GMP requirements as well as Executive Decree No. 91-05 of 19 January 1991 (Decree, 1991) relating to hygiene and safety in the workplace. Laboratories performing batch release are subject to periodic inspections and GMP certification by the Agence Nationale des Produits Pharmaceutiques (ANPP), the national competent authority for pharmaceutical quality oversight.

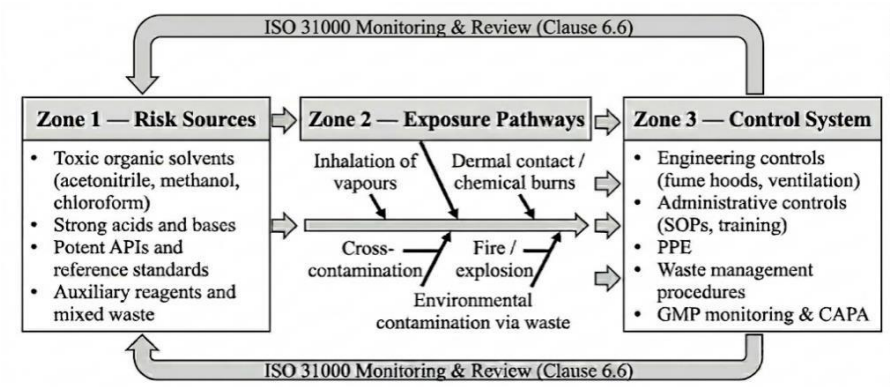
1.2.2 Chemical Toxic Risks in Laboratory Operations: How the Laboratory Deals with Hazards

The daily operations of a physico-chemical quality control laboratory involve the routine manipulation of a broad spectrum of hazardous substances. These include flammable and toxic organic solvents such as acetonitrile, methanol, and dichloromethane; strong mineral and organic acids; potent APIs and reference standards, some with genotoxic or endocrine-disrupting potential; and a range of auxiliary reagents whose interaction products may generate

secondary hazards (INRS, 2016). (Fatemi, Dehdashti, & Jannati, 2022) in a case-series study conducted across five chemical laboratories, classified these hazards on a five-level scale and found that health-risk ratings of "moderate" to "very high" applied to 9.3% of health hazards and 20.4% of safety hazards, with strong acids and formaldehyde among the most critical substances.

The laboratory deals with these chemical hazards through a layered system of controls that this study seeks to map, evaluate, and optimise. The primary risk categories encountered are: inhalation of vapours during sample preparation or solvent evaporation; dermal contact and chemical burns during reagent preparation; cross-contamination between samples or between reagent batches, which may compromise analytical validity; fire and explosion hazards arising from the storage or use of flammable chemicals; and environmental contamination through inadequate waste segregation or disposal (Occupational Safety and Health Administration, 2012) (United States Environmental Protection Agency, 2008), (Bevilacqua, et al., 2023) documented that uncontrolled occupational exposure in pharmaceutical analytical laboratories can lead to acute intoxication, chronic organ damage, and long-term carcinogenic effects, reinforcing the need for systematic risk management rather than reactive incident response.

Figure 1: Schematic representation of chemical risk generation and management in a veterinary physico-chemical quality control laboratory.



Source: by author, based on (OSHA, 2012), (INRS, 2016), and (Bevilacqua, et al., 2023)

2. Risk Management According to ISO 31000:2018

2.1 Fundamental Concepts and Definitions

Risk management is a structured, systematic, and iterative process designed to identify, analyse, evaluate, and treat risks in order to minimise adverse effects and support the achievement of organisational objectives. (Hopkin, 2018) describes it as a set of coordinated activities to direct and control an organisation with regard to risk, while (Dionne, 2013) situates it as a discipline that has evolved from a narrow insurance and financial perspective into a comprehensive strategic management tool applicable to operational environments. (Artikis & Artikis, 2015) stress that a solid understanding of foundational concepts is essential before risk management can be effectively implemented in practice.

The following definitions provide the conceptual foundation for this study, grounded in ISO 31000:2018 and supplemented by key authorities in the risk management literature.

Table 2 : Key Risk Management Concepts and Their Definitions

Concept	**Definition**	**Source**
Risk	The effect of uncertainty on objectives; can be positive (opportunity) or negative (threat)	(ISO31000:2018)

Hazard	A source or situation with the potential to cause harm to health, property, or the environment	(Rausand, 2011)
Likelihood (Frequency)	The probability that a hazard will lead to an undesired event; assessed qualitatively or quantitatively	(Hopkin, 2018), (Rausand, 2011)
Severity (Consequence)	The extent and magnitude of harm resulting from the realisation of a risk	(Rausand, 2011)
Detectability	The ability to identify a failure mode or its effects before they cause harm; used in FMECA scoring	(IEC31010:2019)
Criticality	The combined effect of frequency, severity, and detectability, used to prioritise risk treatment actions (C = F × S × D)	(Laarej, Jbilou, Bouatia, Elyadini, & Alami, 2021)
Residual Risk	The risk remaining after treatment measures have been implemented; the level consciously tolerated	(Hopkin, 2018)
Risk Appetite	The amount and type of risk an organisation is willing to accept in pursuit of its objectives	(ISO31000:2018)

Source: *by author*

2.2 The Distinction between Risk Assessment and Risk Management

Although the terms are sometimes used interchangeably in practice, risk assessment and risk management refer to distinct but related concepts that must be clearly differentiated in any rigorous study of laboratory chemical risk governance.

Risk assessment is a specific, bounded component within the broader risk management process. It comprises three sequential steps: risk identification, risk analysis, and risk evaluation ((ISO31000:2018), Clause 6.4, (Rausand, 2011)). Risk assessment provides the technical

evidence base identifying hazards, estimating probabilities and consequences, and determining risk levels but does not by itself include risk treatment, monitoring, or communication. (Solin & Skubincan, 2013) further distinguish between single-dimension risk assessment, which focuses only on the probability of the hazardous event, and multi-dimensional risk assessment, which combines probability with severity and detectability the latter being the approach adopted in this study through the FMECA method.

Risk management, by contrast, is an overarching and iterative process encompassing risk identification, analysis, evaluation, treatment, monitoring, review, and communication (ISO31000:2018). (Aven, 2016) positions risk management as the decision-making layer built upon the analytical foundation of risk assessment. In the context of a physico-chemical quality control laboratory, a laboratory may conduct a thorough risk assessment identifying chemical hazards, calculating criticality, and ranking risks without proceeding to full risk management. Full risk management requires implementing control measures, assigning risk owners, defining risk tolerance levels, and conducting periodic reviews and monitoring. Without these steps, the risk assessment remains an analytical exercise rather than an effective risk management system. This study therefore adopts the ISO 31000:2018 position that risk assessment is necessary but insufficient for effective chemical risk governance.

Table 3 : Distinction between Risk Assessment and Risk Management

Concept	**Scope**	**Key Outputs**
Risk Assessment	Identification, analysis, and evaluation of risks	Risk register, criticality scores, risk matrix, prioritised list of risks
Risk Management	Assessment + treatment + monitoring + review + communication	Action plan, assigned responsibilities, residual criticality, reviewed controls, continuous improvement cycle

Source: *by author*

2.3 ISO 31000:2018: Principles, Framework, and Iterative Process

2.3.1 Historical Development and Scope

ISO 31000 was first published in 2009 as the first globally accepted framework for risk management, developed through a consensus process involving risk professionals from

numerous countries (Purdy, 2010). (Leitch, 2010) observed that (ISO 31000:2009) constituted the first standard to claim universal applicability across all risk types and organisational contexts, thereby reinforcing the credibility of risk management as a globally transferable discipline. (Lalonde & Boiral, 2012a) described the framework as providing a universal structure intended to help organisations integrate risk management into their overall management system in a systematic and comprehensive manner, while also noting that the standard's claim of universal applicability may be challenging in practice due to differing organisational cultures and resource constraints.

A six-year revision process led by ISO/TC 262 (2013–2018) produced the updated ISO 31000:2018, which places greater emphasis on creating and protecting value as the key driver of risk management, and which reinforces principles of continual improvement, stakeholder inclusion, customisation, and consideration of human and cultural factors (International Organization for Standardization, 2018). The standard is designed for use by any organisation regardless of sector, size, or location, and provides guidelines rather than requirements, meaning it is not intended for certification purposes. This affords practitioners the flexibility to tailor its provisions to specific operational contexts a characteristic that makes it particularly well suited to specialised environments such as veterinary pharmaceutical quality control laboratories.

2.3.2 The ISO 31000 Framework: Six Stages

(ISO31000:2018) situates the risk management process within a broader governance framework (Clause 5). This framework is itself an iterative cycle, comprising six interdependent stages:

• Leadership and Commitment (Clause 5.2): Active and visible support from top management is essential to embed risk management into the organisation's culture, objectives, and resource allocation decisions.

• Integration (Clause 5.3): Risk management must be incorporated into all organisational processes, including planning, operations, and performance review, rather than treated as a separate activity.

• Design (Clause 5.4): The framework must be tailored to the organisation's unique risk context, taking into account internal and external factors, stakeholder requirements, and existing quality systems.

• Implementation (Clause 5.5): The designed framework is translated into operational processes, including risk assessment procedures, treatment plans, and communication protocols.

• Evaluation (Clause 5.6): Regular assessment of framework performance and effectiveness, including comparison against stated risk criteria.

• Improvement (Clause 5.7): Continuous refinement based on evaluation findings, incident data, and changes in the operational or regulatory environment.

For a physico-chemical quality control laboratory, the Integration stage is of particular importance: it ensures that risk management becomes embedded in routine analytical operations rather than remaining a periodic, standalone exercise. The Evaluation stage is equally critical, as it provides the mechanism for verifying that implemented control measures remain effective as laboratory equipment, reagents, personnel, and regulatory requirements evolve.

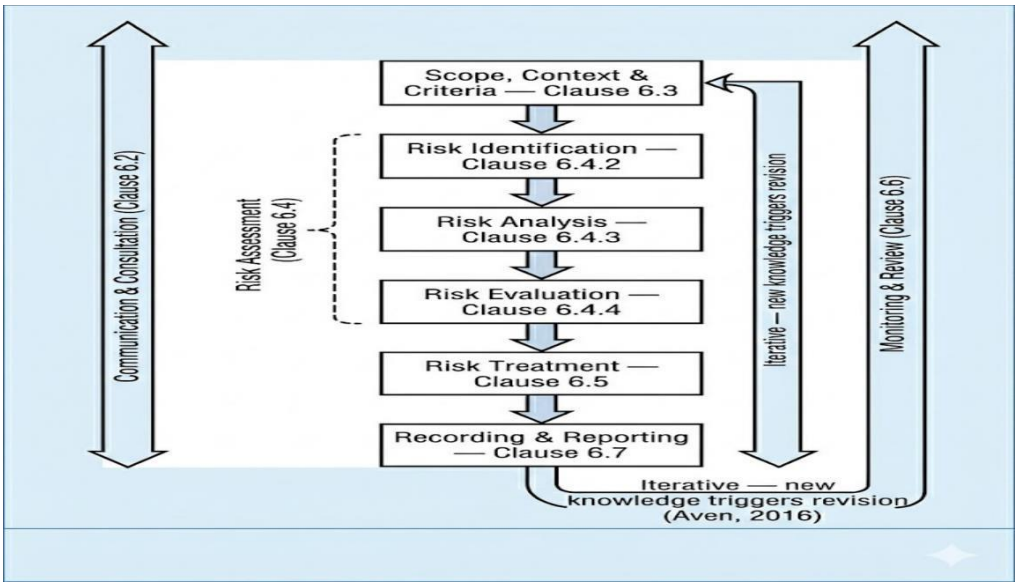
2.3.3 The Iterative Risk Management Process

The risk management process ((ISO31000:2018), Clause 6) is designed as a non-linear, iterative cycle. The ISO technical committee explicitly stated in the 2018 revision documentation that the standard places greater emphasis on the iterative nature of risk management, drawing on new experiences, knowledge, and analysis for the continuous revision of process elements, actions, and controls (ISO, 2018). (Aven, 2016) reinforces this, arguing that effective risk management must continuously update its understanding of risks as new knowledge becomes available a principle directly relevant to laboratory environments where chemical formulations, analytical methods, and exposure scenarios change regularly.

The process begins with defining the scope, context, and criteria (Clause 6.3), followed by the three-stage risk assessment (Clause 6.4), then risk treatment (Clause 6.5). Two parallel, continuous activities communication and consultation (Clause 6.2) and monitoring and review (Clause 6.6) operate across all stages. Recording and reporting (Clause 6.7) creates an auditable documentary history. This structure is directly reflected in the FMECA instrument, which collects pre-treatment and post-treatment criticality data and assigns responsibilities for each corrective action thereby operationalising the full ISO 31000 process within the specific context of a veterinary pharmaceutical quality control laboratory.

Figure 2 below provides a schematic representation of the iterative risk management process as defined by the ISO 31000:2018 standard.

Figure 2 : The ISO 31000:2018 iterative risk management process.



Source: *author's construction based on (ISO31000:2018)(Clause 6) and (Aven, 2016)*

2.4 Stage 1: Establishing the Scope, Context, and Risk Criteria

The first stage of the risk management process requires the organisation to specify the boundaries of its risk management activities, the objectives to be protected, the available resources, and the regulatory requirements that apply ((ISO31000:2018), Clause 6.3). For a veterinary pharmaceutical quality control laboratory, scope definition encompasses the laboratory's analytical workflows, the categories of chemicals handled, the personnel involved, the relevant GMP requirements, and the interface between laboratory operations and production.

External context includes the regulatory environment Algerian GMP legislation, international standards such as ISO 31000 and ICH Q9, and WHO guidelines as well as market expectations, supplier relationships, and environmental obligations. Internal context includes the laboratory's quality management system, documented procedures, analytical equipment, staff competencies, organisational culture, and historical incident data.

Risk criteria the benchmarks against which assessed risks are compared to determine their significance must be derived from this context analysis. For a physico-chemical quality control laboratory, risk criteria may be drawn from occupational exposure limits (OELs) established by (INRS, 2016) or (OSHA, 2012), from internal quality objectives such as maximum acceptable rates of OOS results; from GMP requirements for contamination control; and from environmental regulations governing chemical waste. (Lalonde & Boiral, Managing risks through ISO 31000: A critical analysis., 2012b) caution that the operationalisation of risk criteria can be challenging in practice, particularly in organisations where formal risk appetite

statements are absent or poorly defined, which makes their explicit documentation at the outset of the risk management process especially important.

2.5 Stage 2: Risk Assessment: Identification, Analysis, and Evaluation

2.5.1 Risk Identification

Risk identification (Clause 6.4.2) aims to find, recognise, and describe all risks that might prevent the organisation from achieving its objectives. (Aven, 2016) positions risk identification as the analytical foundation of the entire risk management process: without a comprehensive inventory of potential failure modes, subsequent analysis and treatment will inevitably be incomplete. In the context of a veterinary pharmaceutical quality control laboratory, risk identification must systematically cover four categories of hazard sources: chemical hazards (toxic solvents, corrosive reagents, flammable materials, potent APIs); equipment-related hazards (calibration failures, pressure vessel incidents, electrical faults); procedural hazards (deviations from validated analytical methods, inadequate documentation); and human factors (fatigue, insufficient training, inadequate use of personal protective equipment).

In this study, risk identification was conducted through three convergent methods: semi-structured interviews with the Quality Manager, Quality Control Specialist, and Laboratory Analyst; non-participant observation of laboratory operations over five non-consecutive days; and documentary analysis of Safety Data Sheets (SDS), Standard Operating Procedures (SOPs), incident reports, and existing risk registers. This triangulated approach is consistent with the recommendation in ISO 31000:2018 that risk identification should be conducted iteratively and collaboratively, drawing on diverse knowledge sources.

2.5.2 Risk Analysis

Risk analysis (Clause 6.4.3) involves understanding the nature, sources, and consequences of identified risks, including the effectiveness of any existing controls. In this study, risk analysis is performed using the Failure Mode, Effects, and Criticality Analysis (FMECA) method, which assigns numerical ratings on a scale of 1 to 5 to three dimensions: frequency (F), the probability of occurrence; severity (S), the magnitude of consequences; and detectability (D), the ability to identify the failure before it causes harm. The criticality index is calculated as $C = F \times S \times D$, generating a composite score that reflects the overall risk level of each failure mode.

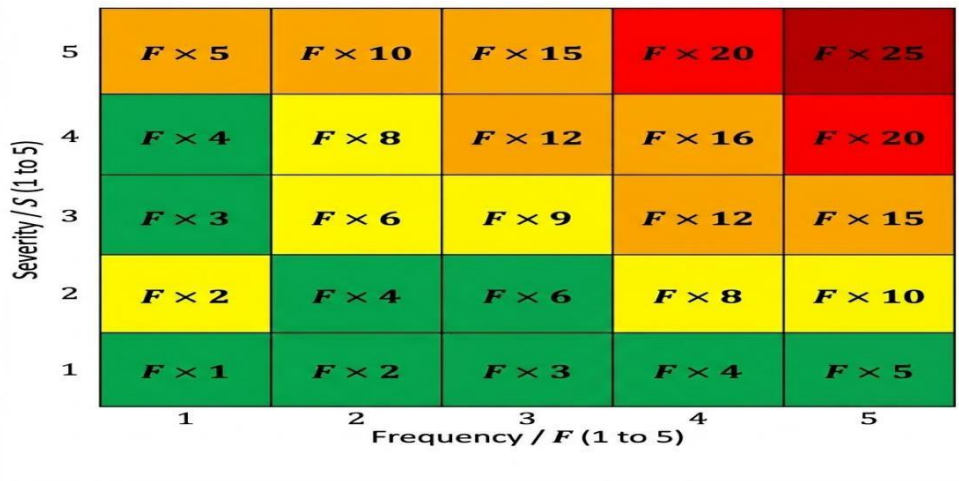
(Kaleem, Koilpillai, & Narayanasamy, 2024), in a review of risk assessment tools in pharmaceutical development, confirmed that FMECA is among the most widely validated

instruments for quality risk management in pharmaceutical contexts, noting that its structured output provides a direct basis for prioritising corrective action and demonstrating risk-based thinking to regulatory inspectors. (Laarej, Jbilou, Bouatia, Elyadini, & Alami, 2021) applied FMECA in a toxicology laboratory and identified 39 failure modes across pre-analytical, analytical, and post-analytical phases, demonstrating the instrument's capacity to capture the full operational cycle of laboratory risk. (El Kara, et al., 2025) further validated the FMECA approach in a drug control laboratory, demonstrating a reduction in average criticality from 31.9 (high) to 10.4 (minor) following the implementation of a structured corrective action plan.

2.5.3 Risk Evaluation

Risk evaluation (Clause 6.4.4) compares the results of risk analysis with the established risk criteria to determine which risks require treatment and with what degree of urgency. In this study, the risk assessment grid uses a 1-to-5 scale for each FMECA dimension, with criticality thresholds distinguishing negligible ($C \leq 10$), minor (11–25), moderate (26-60), critical (61100), and catastrophic ($C > 100$) risk levels. (Aven, 2016) cautions against over-reliance on simple risk matrices when probability estimates are associated with significant epistemic uncertainty, arguing for transparent documentation of the reasoning behind each rating.

Figure 3 : Two-parameter FMECA criticality matrix (F × S).



Source*:* by author *based on the FMECA methodology described in* (El Kara, et al., 2025) *and* (IEC31010:2019)

2.6 Stage 3: Risk Treatment: The 4T Framework

Risk treatment ((ISO31000:2018), Clause 6.5) is the process of selecting and implementing options to address assessed risks. It represents the bridge between analytical findings and

concrete operational change. ISO 31000:2018 identifies several generic treatment options: avoiding the risk, taking or increasing the risk (when beneficial), removing the risk source, changing the likelihood or consequences, sharing the risk with another party, or retaining the risk by informed decision. In practice, these options are synthesised into the "4T" framework (Tolerate, Terminate, Transfer, Treat) which provides a structured and memorable basis for laboratory-level risk treatment decisions (Hopkin, 2018)

Table 4 : The 4T Risk Treatment Framework Applied to a Veterinary Physico-Chemical Laboratory Context

Treatment Option	**Description**	**Application in the Laboratory**
Tolerate (Accept)	Consciously retain the risk because it falls within defined tolerance, or treatment cost outweighs benefit. Requires active monitoring.	Accepting residual risk of buffer solution use after engineering controls are in place; documenting the acceptance decision.
Terminate (Avoid)	Modify processes or objectives to eliminate the risk entirely.	Replacing a carcinogenic solvent with a less toxic validated alternative; discontinuing an unsafe analytical procedure.
Transfer (Share)	Shift financial or operational responsibility to another party.	Contracting licensed hazardous waste disposal; insuring laboratory instruments against accidental damage.
Treat (Mitigate)	Implement controls to reduce frequency, severity, or detectability of the risk.	Installing fume hoods (engineering control); drafting detailed SOPs (administrative control); providing gloves, goggles, and lab coats (PPE).

***Source*:** adapted from Hopkin (2018); laboratory applications by the author

The selection of an appropriate treatment option should be informed by cost-benefit analysis, technical feasibility, and the laboratory's defined risk criteria. Once selected, treatment actions must be documented in the FMECA action plan column, assigned to a named responsible party

(Quality Manager, Quality Control Specialist, or Laboratory Analyst), resourced appropriately, and subjected to verification before being considered operationally effective.

2.7 Stage 4: Monitoring, Review, and Continual Improvement

Monitoring and review ((ISO31000:2018), Clause 6.6) ensure that the risk management process remains current and effective in response to changing operational circumstances. Unlike static risk registers common in earlier regulatory practice, ISO 31000 requires an ongoing cycle of planning, data gathering, analysis, documentation, and feedback. This approach aligns with the Plan-Do-Check-Act (PDCA) cycle embedded in ISO high-level structure frameworks. When laboratory conditions change through new equipment installation, reagent substitution, staff reassignment, or regulatory updates the risk assessment and treatment approach must be revisited.

Continual improvement (Clause 5.7) closes the loop: monitoring findings feed back into the design and implementation stages of the framework, ensuring that lessons learned from incidents, near-misses, and routine observations inform the next iteration of risk identification and analysis. In the laboratory context, this means that the risk management policy, FMECA register, and control checklists should be formally reviewed at defined intervals and whenever a significant change occurs in operations, staffing, or regulatory requirements.

(Power, 2007) warns that organisations may engage in ritualistic risk management that creates an appearance of control without substantive risk reduction. (Lalonde & Boiral, Managing risks through ISO 31000: A critical analysis., 2012b) similarly caution that ISO 31000 may be implemented in a purely formalistic manner satisfying documentation requirements without embedding risk thinking into everyday decisions. Effective implementation therefore requires tailoring the monitoring and review design to the specific operational reality of the laboratory, ensuring that reassessed residual criticality scores reflect real-world control effectiveness rather than mere checklist compliance.

3. Good Manufacturing Practices for Veterinary Physico-Chemical Control Laboratories

3.1 Foundations and Algerian Regulatory Framework

This section examines the regulatory and institutional foundations underpinning the application of Good Manufacturing Practices to veterinary physico-chemical quality control laboratories in Algeria. It proceeds in two stages: the first traces the historical development of GMP requirements and their specific adaptation to the veterinary pharmaceutical sector; the second

analyses the institutional mechanisms through which the Algerian competent authority enforces these requirements, with particular attention to the certification and inspection functions of the ANPP. Together, these two dimensions establish the normative architecture within which chemical risk management practices in Algerian veterinary laboratories are situated and assessed.

3.1.1 Evolution of GMP and Specificities for Veterinary Medicines

Good Manufacturing Practices constitute the mandatory quality assurance system for the manufacture and control of veterinary medicinal products. The core GMP requirements for veterinary medicines in Europe were codified in (Commission Directive 91/412/EEC, 23 July 1991) which laid down principles covering personnel, premises, equipment, documentation, production, quality control, and self-inspection. Article 11 of the Directive required each manufacturer to maintain an independent quality control department, adequately staffed and equipped, responsible for all testing of starting materials, packaging materials, and finished products. Article 13 imposed retention of batch samples for at least one year after the expiry date a requirement that directly influences sample management, storage conditions, and documentation systems in physico-chemical laboratories.

For over three decades, veterinary GMP has been governed within the EudraLex Volume 4 framework. However, from 16 July 2026, a dedicated regulatory framework will take effect in the European Union: Commission Implementing (Commission Implementing Regulation (EU), 2025) on GMP for veterinary medicinal products and Commission Implementing Regulation (EU) 2025/2154 on GMP for active substances used in veterinary products ((European Commission, 2025a). These regulations introduce legally binding language and reinforce requirements for analytical method validation, data integrity (ALCOA+ principles), reference standard management, stability testing, and OOS investigation with root cause analysis. It must be emphasised that these EU regulations are not currently directly applicable in Algeria; however, they represent the international best practice benchmark against which Algerian regulatory development is assessed.

(Al Azawei, Loughrey, Surim, Connolly, & Naughton, 2025) in a scoping review of GMP inspection management, identified three critical phases of GMP inspection pre-inspection, execution, and post-inspection and highlighted that effective inspection readiness requires laboratories to maintain continuous, documented risk management rather than reactive compliance. This finding reinforces the argument that ISO 31000-based risk management is not merely a theoretical supplement to GMP but a practical prerequisite for sustained regulatory compliance.

3.1.2 The Role of the ANPP in GMP Certification and Inspections in Algeria

In Algeria, the legal basis for GMP of veterinary medicines is Executive (Executive Decree No. 90-240, 4 August 1990), as amended by (Executive Decree No. 23-124 of 18 March 2023). The decree specifies requirements for the manufacture, sale, and control of veterinary medicinal products. For quality control laboratories, the key provisions are: Article 11, which requires the laboratory to be functionally independent from production and to have a designated responsible person, adequate facilities, and documented testing procedures; Article 12, which mandates a controlled documentation system for all test methods, specifications, and sampling procedures; and Article 13, which requires batch sample retention for at least one year beyond the expiry date.

The Agence Nationale des Produits Pharmaceutiques (ANPP), operating under the supervision of the Ministry of Pharmaceutical Industry, is the competent authority responsible for GMP certification and inspections across all pharmaceutical establishments in Algeria, including veterinary medicine manufacturers (ANPP, 2025). Its inspection remit covers the full scope of quality management system elements: quality manuals and SOPs, document control, deviation and CAPA management, personnel training records, premises and equipment qualification, analytical method validation, reference standard management, data integrity, and self-inspection programmes.

The ANPP has progressively expanded its territorial presence: the inauguration of regional annexes in Oran (December 2023) and Constantine (February 2026) the latter including a dedicated animal experimentation laboratory branch reflects the agency's strategic commitment to strengthening veterinary pharmaceutical control infrastructure (RadioAlgerienne, February 2, 2026). For a veterinary pharmaceutical quality control laboratory in Algeria, the ANPP GMP certification cycle involves: submission of a dossier; documentary review; on-site inspection by ANPP inspectors; and a certification decision with a two-year validity, subject to follow-up inspections.

able 5 : *Key ANPP GMP Inspection Focus Areas for a Physico-Chemical Quality Control Laboratory*

Inspection Area	**Key Verifiable Elements**
Quality System	Quality manual, SOPs for all test methods, document control, change control, deviation and CAPA management

Personnel	Organisational chart, job descriptions, initial and ongoing training records, health surveillance records
Premises and Equipment	Calibration certificates (HPLC, balances, pipettes), instrument qualification, equipment logbooks, preventive maintenance schedules
Testing Operations	Adherence to validated methods, system suitability criteria, certified reference standards, OOS investigation documentation
Chemical Safety	Storage conditions for toxic and flammable substances, SDS availability, PPE provision and usage records, waste management procedures
Sample Management	Chain of custody documentation, storage conditions (temperature, security), retention sample programme
Data Integrity	Audit trails for electronic systems, raw data storage, access controls, backup procedures, ALCOA+ compliance
Self-Inspection	Scheduled internal audits with documented findings, CAPA follow-up, effectiveness verification

***Source**: Adapted from Executive Decree No. 23-124, 2023; Ministerial Decree No. 21, 2025*

3.1.3 Integration of Risk-Based Thinking into GMP for the Quality Control Laboratory

The GMP requirements described above are not a static checklist to be satisfied reactively; they must be implemented through the risk-based thinking promoted by ICH Q9 and ISO 31000. For a veterinary physico-chemical quality control laboratory, this means applying risk stratification principles across all regulated activities. Risk-based validation prioritises analytical methods by their criticality: a high-risk test for a toxic impurity with patient-safety implications demands more rigorous validation than a low-risk test for a non-hazardous excipient property (Kaleem, Koilpillai, & Narayanasamy, 2024). Risk-based calibration intervals allow equipment maintenance frequencies to be adjusted according to historical performance, usage intensity, and potential impact on product quality. Risk-based environmental monitoring determines sampling locations and frequencies in the laboratory based on assessed contamination risk to samples and products.

(Arunagiri, Kannaiah, & Vasanthan, 2024) in a comprehensive review of CAPA frameworks in pharmaceutical quality assurance, demonstrated that the integration of risk-based thinking into CAPA systems enables a shift from reactive incident management to proactive quality governance a shift that is both required by modern GMP frameworks and directly supported by the ISO 31000 principles.

4. Integration of ISO 31000, ICH Q9, GMP, and Complementary Analytical Tools

4.1 Articulation between ISO 31000, ICH Q9, and GMP

The relationship between ISO 31000, ICH Q9, and GMP is not one of simple hierarchy or redundancy, but rather one of functional complementarity across distinct levels of risk governance. Understanding both the convergences and the structural differences between these frameworks is a necessary prerequisite for designing an integrated model that is simultaneously coherent in theory and operational in practice. The following subsection undertakes this comparative analysis, before subsequent subsections examine how the complementary analytical tools FMECA, Ishikawa analysis, and CAPA serve as the methodological instruments through which the integrated framework is operationalised at the laboratory level.

4.1.1 Complementarity and Differences between the Frameworks

The articulation between ISO 31000, ICH Q9, and Good Manufacturing Practice forms the conceptual bridge between general risk management principles and their specific application in regulated veterinary pharmaceutical environments. Each framework occupies a distinct but complementary level of the risk governance architecture.

ISO 31000:2018 provides the strategic and principles-based governance layer: it defines risk as "the effect of uncertainty on objectives," offers a universal framework applicable to any organisation, and emphasises integration, continual improvement, and stakeholder inclusion. ICH Q9 (Quality Risk Management), originally issued in 2005 and substantially revised in 2023 as ICH Q9(R1), adapts the general principles of risk management to the pharmaceutical industry with a dedicated focus on product quality and patient safety. It defines quality risk management as "a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across its lifecycle" (International Council for Harmonisation., 2023) GMP then translates risk-based thinking into mandatory regulatory requirements for pharmaceutical manufacture and quality control, providing the binding operational framework within which ISO 31000 and ICH Q9 principles are implemented.

Table 6 : Complementarity between ISO 31000:2018, ICH Q9 (R1), and GMP

Aspect	**ISO 31000:2018**	**ICH Q9(R1)**	**GMP (EudraLex / WHO)**
Scope	Any organisation, any risk type	Pharmaceutical industry; product quality and patient safety	Manufacturing and quality control of pharmaceutical products
Risk Definition	Effect of uncertainty on objectives (threats and opportunities)	Combination of probability of harm and severity of harm	Operationalised through specific requirements (OOS, CAPA, deviations)
Primary Tools	Context analysis, risk matrix, iterative process	FMEA, HACCP, risk ranking; hazard identification	SOPs, validation, calibration, batch records, inspections
Relationship to GMP	Provides governance architecture	Explicit bridge between ISO 31000 and GMP	Mandatory regulatory framework
Certification	Not certifiable (guidelines)	Not certifiable (guidelines)	Certifiable (GMP certificates issued by regulatory authorities)

Source: *by the author*

A key conceptual link between ISO 31000 and ICH Q9 is the principle of risk-based thinking. ISO 31000 advocates for integrating risk management into all organisational processes, which aligns directly with the GMP requirement to apply scientific and risk-based thinking across the product lifecycle (ICH Q10, 2008). Both frameworks share a commitment to systematic risk identification, assessment, control, and review, and both recognise that the level of effort invested in risk management should be proportionate to the level of risk a principle directly operationalised in the criticality-based prioritisation structure of the FMECA instrument used in this study.

4.1.2 ICH Q9 (R1) as the Bridge between ISO 31000 and GMP

ICH Q9 serves as the essential bridge that translates the generic principles of ISO 31000 into a practical, auditable framework for pharmaceutical manufacturing. It adapts the general risk management concepts to the specific regulatory context of GMP, where compliance is mandatory. The 2023 revision, ICH Q9 (R1), reinforced this bridge by adding three new sections: Section 5.1 on formality in quality risk management; Section 5.2 on risk-based decision-making; and Section 5.3 on managing and minimising subjectivity in risk assessments (ICH, 2023) These additions directly address four previously identified weaknesses in pharmaceutical quality risk management: high levels of subjectivity in risk assessments, inadequate management of supply and product availability risks, poor understanding of appropriate formality levels, and insufficient clarity about risk-based decision-making criteria. The revised (ICH Q9 (R1), 2023) notably changes the terminology from "risk identification" to "hazard identification," aligning more closely with occupational safety and risk science literature (Rausand, 2011). This change underscores the importance of identifying specific hazardous agents such as the toxic substances routinely handled in a veterinary pharmaceutical quality control laboratory before proceeding to risk estimation. The revision also provides guidance on managing subjectivity by recommending structured processes, multi-disciplinary teams, and transparent documentation.

4.2 Complementary Analytical Tools

4.2.1 FMECA: Failure Mode, Effects, and Criticality Analysis

Failure Mode, Effects, and Criticality Analysis (FMECA, also referred to as FMEA in contexts where the criticality dimension is embedded in the scoring formula) is an inductive risk assessment method that systematically analyses each process step by asking: how can this step fail? What happens if it fails? Why does it fail? (IEC31010:2019). In pharmaceutical contexts, FMECA assigns three ratings frequency (F), severity (S), and detectability (D) and calculates a criticality index $C = F \times S \times D$. Higher criticality values indicate higher priority for corrective action.

(Laarej, Jbilou, Bouatia, Elyadini, & Alami, 2021) applied FMECA in a toxicology laboratory and identified 39 risk scenarios across pre-analytical, analytical, and post-analytical phases. The analytical phase contained the highest number of risks (18) with the highest criticality scores; critical risks included inappropriate sampling (C = 27) and contamination of hygiene personnel (C = 32). After implementing corrective actions, the laboratory successfully reduced the most critical risks. (El Kara, et al., 2025) applied FMECA to a drug control laboratory and identified

53 failure modes, of which 33 were of major criticality (C > 25), yielding an average criticality of 31.9. Following the implementation of corrective and preventive actions including PPE provision, personnel training, procedure updates, NIOSH hazard classification lists, and dedicated waste management containers the average criticality dropped to 10.4, demonstrating the instrument's utility as a continuous improvement tool.

In applying FMECA to a veterinary pharmaceutical physico-chemical quality control laboratory, the matrix analyses the most critical toxic substances handled in routine operations, producing a 15-column action-oriented register that connects pre-treatment criticality scores to specific corrective measures, responsible parties, and post-treatment residual criticality. (Kaleem, Koilpillai, & Narayanasamy, 2024) confirmed that FMECA is among the most widely validated instruments for quality risk management in pharmaceutical development, noting that its structured, quantified output provides a direct basis for risk-based regulatory compliance demonstrations.

4.2.2 The Ishikawa Diagram and the 5 Whys

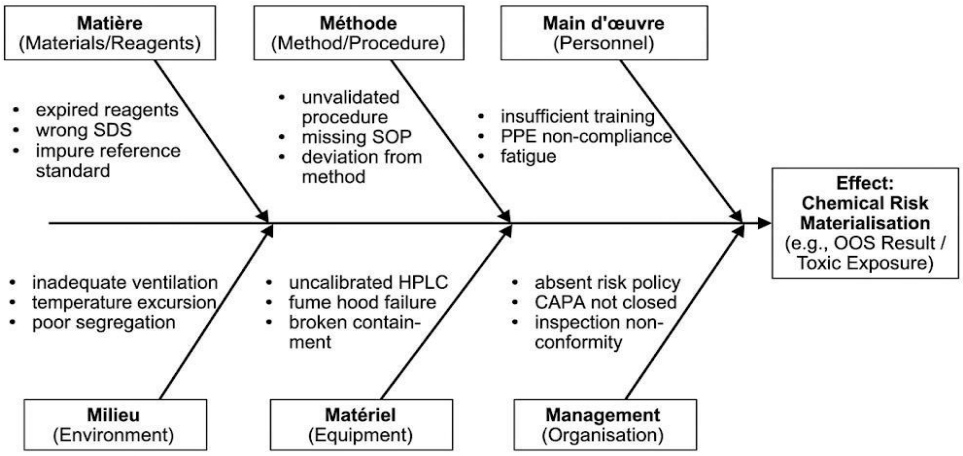
The Ishikawa diagram (fishbone diagram) and the 5 Whys technique are complementary root cause analysis tools that probe the systemic causes underlying identified failure modes. Both are listed among recommended risk assessment techniques in IEC 31010:2019, and both are expected by major pharmaceutical regulatory bodies including the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) in deviation and OOS investigations.

The Ishikawa diagram, developed by Professor Kaoru Ishikawa in the 1960s, organises potential causes of a problem into logical categories along a horizontal "spine" pointing to the identified effect. In pharmaceutical and laboratory quality investigations, the standard 5M classification is used: Matière (materials/reagents), Milieu (environment), Méthode (methods/procedures), Matériel (equipment), and Main d'oeuvre (personnel/workforce). Some applications add a sixth category: Management (organisational governance). This structured brainstorming tool enables multi-disciplinary teams to map the full causal landscape of a failure mode before selecting targeted corrective actions.

(El Kara, et al., 2025) explicitly applied the Ishikawa diagram and 5M method in their drug control laboratory study, constructing detailed cause-and-effect maps for each critical failure mode. This analysis identified root causes including the absence of hazardous drug identification systems, insufficient staff training, lack of written procedures, and inadequate

personal protective equipment findings consistent with commonly observed gaps in pharmaceutical quality control laboratories operating under resource and regulatory constraints. The 5 Whys technique iteratively deepens causal analysis by asking "Why?" five times (or as many as necessary) to move from the symptomatic surface failure to the underlying systemic cause. In practice, the Ishikawa diagram is used first to map all possible cause categories, and the 5 Whys is then applied to the most probable causes identified in the fishbone to determine the exact root cause amenable to systemic correction. While the Ishikawa diagram constitutes a recognised and widely applied tool in pharmaceutical risk management, the present study operationalises root cause identification through qualitative data triangulation combining field observation, semi-structured interviews, and documentary analysis rather than formal fishbone construction, given the constraints of a single-site dissertation study.

Figure 4 : Generic Ishikawa (fishbone) diagram structure using the 5M+1 classification for root cause analysis in a physico-chemical quality control laboratory



Source: *compiled by the author* Adapted from *(El Kara, et al., 2025)* and *(IEC31010:2019)*

4.2.3 CAPA: Closing the Risk Management Loop

Corrective and Preventive Action (CAPA) represents the operational closure of the risk management cycle. (Arunagiri, Kannaiah, & Vasanthan, 2024) define CAPA as a dual-loop mechanism within the pharmaceutical quality management system: corrective actions address the root causes of specific identified problems to prevent recurrence; preventive actions proactively mitigate potential future risks before they materialise. Together, they transform the analytical outputs of FMECA and Ishikawa analysis into a structured, documented, and time-bound improvement programme.

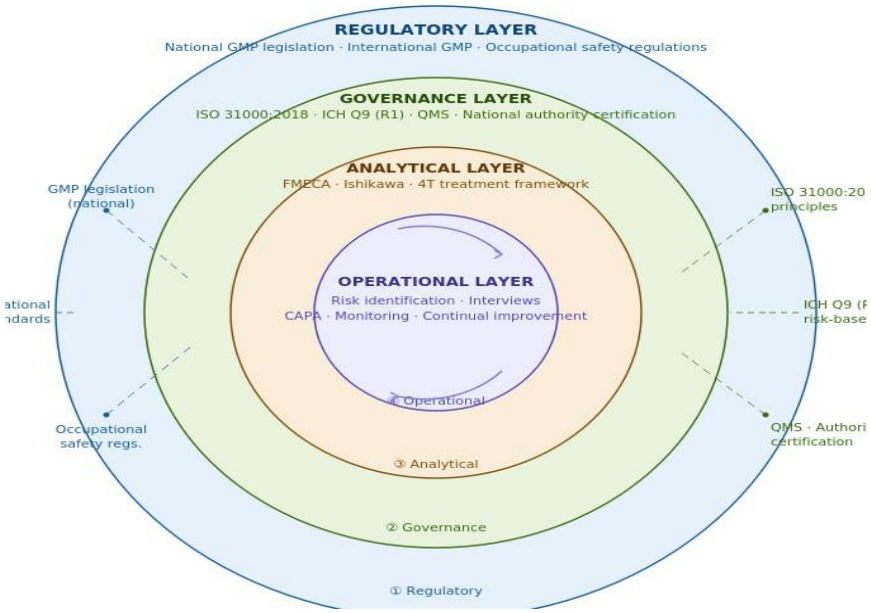
In a GMP-regulated veterinary pharmaceutical quality control laboratory, CAPA must be linked directly to the risk register produced by FMECA. For each critical failure mode, the CAPA plan

specifies the proposed control measure, the responsible party, the expected completion date, the effectiveness criteria, and the residual criticality following implementation. Both (Laarej, Jbilou, Bouatia, Elyadini, & Alami, 2021) and (El Kara, et al., 2025) integrated FMECA outputs into CAPA plans and demonstrated measurable reductions in criticality. This creates the closed-loop improvement system that ISO 31000:2018 and ICH Q9 (R1) require: risk assessment feeds the action plan; the action plan drives implementation; implementation is followed by reassessment; and the results are documented and reviewed completing one iteration of the continual improvement cycle.

4.3 Conceptual Model: How This Study Operationalises the Framework

Figure 3 below synthesises the conceptual architecture of this study and illustrates how the laboratory deals with chemical risks through the integrated application of ISO 31000:2018, GMP requirements, ICH Q9 principles, and the complementary analytical tools.

Figure 5: Conceptual architecture of the study integrated application of ISO 31000:2018, GMP requirements, ICH Q9 principles, and complementary analytical tools for chemical risk management in a veterinary pharmaceutical quality control laboratory.



Source: *compiled by the author*

The model operates in four interconnected layers. The regulatory layer (outer ring) establishes the normative requirements: national GMP legislation, international GMP standards, and occupational safety regulations define the minimum obligations any veterinary pharmaceutical quality control laboratory must meet. The governance layer (second ring) provides the strategic architecture: ISO 31000:2018 principles and ICH Q9 (R1) risk-based thinking are embedded

into the laboratory's quality management system, operating under the oversight of the competent national authority's certification and inspection process. The analytical layer (third ring) encompasses the specific risk assessment and root cause analysis instruments: FMECA for criticality assessment and prioritisation, qualitative triangulation to identify root causes, and the 4T treatment framework to guide action selection. The operational layer (inner ring) represents the laboratory's actual risk management practices and their continuous improvement: risk identification through interviews, observation, and documentary analysis; CAPA implementation by designated responsible parties; residual criticality monitoring; and continual improvement through periodic review.

This conceptual framework has laid the theoretical and regulatory groundwork needed to understand and improve how chemical toxic risks are managed in a veterinary pharmaceutical physico-chemical quality control laboratory. Through four interconnected sections the laboratory's chemical risk profile, the ISO 31000:2018 iterative process, the Algerian GMP regulatory framework, and the integrated model bringing together FMECA, and CAPA a clear and operational picture emerges: one in which risk identification, criticality analysis, treatment, and continual improvement are not isolated steps but parts of a unified system, firmly rooted in both international standards and the concrete regulatory reality of the veterinary pharmaceutical sector.

CHAPTER II: METHODOLOGICAL AND ORGANIZATIONAL FRAMEWORK

This chapter is structured into two main parts that address the fundamental dimensions of the research. The first part presents the methodological framework of the study, detailing the approaches adopted for data collection and analysis. The second part is dedicated to the presentation of the host company, with particular emphasis on its organizational structure and operational processes.

In this manner, the chapter establishes the essential foundations required for a clear understanding of the methods and procedures employed to achieve the objectives of the study

Section 1: Methodological Framework

In this section, we present the methodology adopted in this study, as well as the methods and tools used for data collection and analysis to achieve the research objectives. Methodology is defined as "the logical procedures of a science, the set of specific practices it implements to ensure that the progression of its arguments and theories is clear, evident, and irrefutable" (Quivy, Van Campenhoudt, & Marquet, 2017)

Consequently, in any scientific research process, presenting the chosen methodology is essential, as it clarifies the steps taken to gather the data required for the study and helps justify the results obtained.

1. Type of research:

This study adopts a qualitative, descriptive and analytical single-case study design. According to (Yin, 2018), the case study method is particularly appropriate for examining a contemporary phenomenon in depth within its real-life context, especially when the boundaries between the phenomenon and the context are not clearly distinct. (Thiétart, et al., 2014) further emphasise the relevance of this approach in management research for analysing complex organisational practices shaped by specific contextual factors.

The case under investigation is the physicochemical quality control laboratory of CEVA *«Santé Animale»* Algeria. This research adopted a single case study approach due to limited time frame and requirement for detailed analysis of chemical risk management within the industrial sector in Algeria.

The research combines a descriptive mapping of chemical substances, exposure situations and existing controls with an analytical evaluation of root causes and compliance with ISO 31000:2018 and Good Manufacturing Practices (GMP). Data collection and analysis were

performed through the triangulation of semi-structured interviews, direct observation, and documentary analysis.

This methodological design is fully consistent with the dissertation objectives, which seek not only to identify and evaluate chemical risks but also to propose practical, context-specific improvement measures for CEVA *«Santé Animale»* Algeria.

2. Methodological approach:

Selecting an appropriate approach for scientific research is crucial, as it greatly affects the relevance and validity of the results obtained. In field studies, both qualitative and quantitative approaches are commonly employed by researchers in the social and management sciences as methods for data collection and analysis (Samlak, 2020) this study adopts a qualitative research approach. Qualitative research is especially well-suited when the goal is to explore, understand, and interpret complex real-life phenomena in their natural context, rather than simply measuring or quantifying them (Samlak, 2020); (Dicko, 2019)). In keeping with this approach, a single-case design was adopted. This design fully meets the requirements of a monographic study focused on a single organization, as it allowed us to conduct a thorough and in-depth examination of chemical risk management practices in one resource-constrained Algerian industrial setting, particularly given the limited time available for the research.

The qualitative approach was selected because this research seeks to gain an in-depth understanding of chemical risk management practices in the physicochemical quality control laboratory of CEVA *«Santé Animale»* Algeria. It enables the researcher to examine the perceptions and lived experiences of the key actors involved the Quality Manager, Quality Control Specialist and Laboratory Analyst– to identify the root causes of chemical risks, and to propose practical, context-adapted solutions that align with the operational and regulatory realities of the company. As emphasised by (Ndinga, 2018), qualitative methods are especially valuable in management sciences when the objective is to analyse organisational practices shaped by contextual and human factors.

This study is rooted in the pragmatist paradigm, which considers that scientific knowledge is best produced through the practical consequences of research and the integration of theory with real-world action (Kontzler, 2023). This orientation supports the use of multiple qualitative data sources and focuses on producing insights that can directly contribute to improving professional practices in the laboratory.

The qualitative approach is fully consistent with the single-case study design adopted in this research. It allows for rich, contextual, and detailed insights that would be difficult to obtain

through quantitative methods alone. Furthermore, it facilitates the triangulation of data collected through semi-structured interviews, direct (participant) observation, and documentary analysis, thereby strengthening the credibility and depth of the findings.

3. Data collection tools and techniques

3.1 Interviews

According to (Saunders, Lewis, & Thornhill, 2019), an interview can be defined as "a purposeful discussion between two or more people, designed to collect data on a specific topic in order to understand the meanings that participants attach to phenomena in their social world". Three main types of interviews are commonly distinguished in qualitative research (Quivy, Van Campenhoudt, & Marquet, 2017) (Blanchet & Gotman, 2010)

Structured (directive) interview: follows a rigid and predefined questionnaire with closed questions, allowing limited flexibility.

Semi-structured interview: based on an interview guide containing mainly open-ended questions, offering both structure and flexibility for in-depth exploration.

Unstructured (non-directive or free) interview: a free-flowing conversation without a prepared guide, resembling a natural discussion.

In this study, the semi-structured interview was chosen. This choice is justified because it enables participants the Quality Manager, Quality Control Specialist and Laboratory Analyst to express themselves freely about their experiences and perceptions of chemical risks, while the interview guide ensures the discussion remains focused on the research objectives. This approach is particularly suitable for describing risk management practices and identifying challenges encountered in daily laboratory operations (N'da, 2015). Furthermore, semi-structured interviews are widely recommended in qualitative research when the aim is to gain rich, contextual insights into complex social or organisational phenomena without imposing excessive constraints on respondents (e.g., (Kallio, Pietilä, Johnson, & Kangasniemi, 2016); (Adams, 2015)).

-Interview Guide

A semi-structured interview guide was developed in advance to direct the discussion while preserving the flexibility essential to this qualitative approach. The guide was structured around five main themes, derived directly from the risk management principles of ISO 31000:2018 and the requirements of Good Manufacturing Practices (GMP) applicable to veterinary pharmaceutical products:

-Perception of chemical risks in the laboratory.

-Current practices of chemical risk identification and assessment.

-Incidents, near-misses, and practical difficulties encountered.

-Training, personal protective equipment (PPE), and existing control measures.

-Suggestions for improvement and prevention.

These themes were selected to cover both participants' subjective perceptions and the objective operational realities of chemical risk management in the physicochemical quality control laboratory of CEVA «Santé Animale» Algeria. Under each theme, a series of open-ended questions and follow-up probes were prepared (e.g., "How do you perceive the chemical risks present in your daily laboratory activities?" or "What difficulties have you encountered when applying risk assessment procedures in practice?").

The development of the interview guide followed a systematic process recommended in the qualitative research literature (Kallio, Pietilä, Johnson, & Kangasniemi, 2016), 2016 (N'da, 2015)). This involved reviewing the key standards ((ISO31000:2018)and GMP), aligning the themes with the specific research objectives, drafting open-ended questions, and refining the structure using a funnel approach starting with broad perceptions before progressing to specific operational challenges and improvement suggestions (Saunders, Lewis, & Thornhill, 2019).

During the interviews, the guide was used flexibly: the order and depth of questions were adapted according to the natural flow of the conversation and each participant's responses. This adaptability is one of the main advantages of semi-structured interviews, allowing the collection of rich and nuanced contextual data. On average, each interview lasted between 35 and 50 minutes. (The complete interview guide is presented in Appendix B.)

Sampling

Three experts were selected with care as interviewees according to their competencies and their skills within the area studied. The present research relies on a purposeful sampling methodology in which subjects are purposely selected in accordance with the criteria most pertinent to the objectives of the research (Patton, 2015). These criteria included these professionals' professional experience, scientific knowledge and their day-to-day direct participation in chemical risk management or in managing hazardous substances in the physico-chemical quality control laboratory.

A sample size of three was adopted since it is an appropriate number given each participant's role. They represented the different levels involved in the management of chemical risks: Quality Control Manager (at strategic/ supervisory level); Quality Control Specialist (at technical/procedural level) and Laboratory Analyst (hands-on, operational level). In this way,

by collecting data from several hierarchical points of view, it will be possible to obtain a richer interpretation of results and therefore perform a better triangulation (Yin, 2018). These choices allow obtaining precise data, related to the objectives of this research.

Table 7. Persons Interviewed

Number	Name (anonymized)	Position	Date	Duration
1	[x]	Quality Control Manager	17/04/2026	45 min
2	[y]	Quality Control Specialist	17/04/2026	35 min
3	[Z]	Laboratory Analyst	17/04/2026	40 min

Source: *elaborated by the author according to interviews data*

3.2 Observation

According to (Allard-Poesi & Perret, 2014), observation is "a data collection method by which the researcher directly observes, visually, processes or behaviors taking place in an organization, over a delimited period of time."

In qualitative research, three main forms of observation are commonly distinguished: participant observation (in which the researcher takes part in the activities), non-participant observation (in which the researcher observes without intervening), and structured observation (based on a predefined grid) (Creswell & Poth, 2018), (Flick, 2018).

In this study, participant observation was chosen. This approach was adopted to allow the researcher to become directly immersed in the daily activities of the physicochemical quality control laboratory of CEVA *« Santé Animale »* Algeria, thereby gaining deeper, first-hand insight into the actual practices of handling toxic substances. Participant observation enables the researcher to experience the professional context from within, generating richer and more nuanced data than purely external observation would permit, as it captures tacit knowledge, informal routines, and contextual dynamics that may remain invisible to an outside observer (Denzin, 2018), (Tracy, 2019). This form of observation is particularly appropriate in organizational settings where understanding real, everyday practices requires the researcher to be present as an active member of the studied environment (Bryman, 2016), (Leavy, 2017).

Observations were conducted over five non-consecutive days, during which the researcher actively participated in laboratory activities alongside the technicians, while simultaneously recording data in a systematic manner. An observation grid, developed in alignment with the risk management principles of ISO 31000:2018 and the requirements of Good Manufacturing

Practices (GMP) applicable to veterinary pharmaceutical products, was used to systematically record the following elements:

- Wearing and proper use of personal protective equipment (PPE), including gloves, masks, goggles, and lab coats.
- Compliance with procedures for handling toxic products.
- Condition and effective use of fume hoods and other containment equipment.
- Chemical waste management practices.
- Any observed risky behaviors or deviations from established safety protocols.

Handwritten field notes were taken during and immediately after the observation sessions to capture additional contextual details, informal interactions, and situational nuances that the grid alone could not fully record. It is acknowledged that participant observation carries an inherent risk of researcher influence on the observed environment; however, this limitation was mitigated through reflexive awareness and by maintaining a systematic and structured recording approach throughout the fieldwork (Creswell & Poth, 2018), (Flick, 2018).

The data collected through participant observation were triangulated with the findings from the semi-structured interviews and documentary analysis. This methodological triangulation strengthened the credibility, reliability, and depth of the overall findings (Saunders, Lewis, & Thornhill, 2019), (Quivy, Van Campenhoudt, & Marquet, 2017)

Figure 6 : Extract from GMP Compliance Checklist

	GMP Compliance Checklist			**Information sheet** **Version N :03** **Elaborate by: Celina Magraoui**
GMP Criterion	**Description**	**Compliance**	**Classification**	**Observations / Findings**

Source: *Appendix A*

3.3 Documentary Analysis

Documentary analysis was one of the key data collection methods used in this study. It consisted of the systematic collection and critical examination of various documents in order to understand the current chemical risk management practices in the physicochemical quality control laboratory of CEVA *« Santé Animale »* Algeria.

This analysis was based on three main categories of sources:

a) Academic resources Books, scientific articles, and theses consulted through the library of the École Nationale Supérieure de Management (ENSM) and specialized databases (SNDL,

Google Scholar, ResearchGate). These sources provided the theoretical and methodological foundations of ISO 31000 and chemical risk management in pharmaceutical laboratories.

b) Normative and regulatory documents

The main international standards and guidelines were analysed, namely:

ISO 31000:2018 Risk management Guidelines (International Organization for Standardization, 2018)

ICH Q9(R1) Quality Risk Management (ICH Harmonised Guideline, 2023)

WHO Good Manufacturing Practices for veterinary medicinal products (World Health Organization, 2019 b)

These documents served as the reference framework to evaluate the compliance of CEVA's practices

c) Internal company documents

with the authorisation of the Quality Manager, the following internal documents of CEVA *«Santé Animale »* Algeria were examined:

- Safety Data Sheets (SDS) for toxic chemical substances (solvents, hormones, cytotoxics).
- Standard Operating Procedures (SOPs) related to chemical handling, storage, cleaning, and waste management.
- Risk registers and previous risk assessments.
- Incident and near-miss reports.
- Personnel training records.

This documentary analysis allowed the researcher to compare official procedures with actual laboratory practices and provided essential data for the identification and evaluation of chemical risks presented in Chapter 3. The findings were triangulated with data from semi-structured interviews and direct observation to increase the reliability of the results (Bowen, 2009) and (Merriam & Tisdell, 2016).

4. Data processing and analysis:

Following the completion of the interviews carried out with the different informants, and after obtaining all the data from direct observations, it became necessary to undertake the stage of data analysis. This step is important in terms of the interpretation of results, especially regarding risk evaluation and management, with regard to handling eight toxic chemical substances in the quality control lab of CEVA *«Santé Animale»* Algeria.

4.1. Failure mode, Effects and Criticality Analysis (FMECA) matrix

The data gathered during the on-site visit were used to construct the FMECA matrix, designed to systematically identify, evaluate, manage, and monitor the risks associated with handling the eight most hazardous chemical substances in the laboratory. The FMECA matrix takes the form of a table comprising 15 columns, described as follows:

1) Toxic substances: This column presents the 8 toxic substances analyzed, considered as the most critical products in the laboratory.
2) Failure modes: This column lists the potential failures that may affect the handling of each toxic substance.
3) Risk description: This column provides brief descriptions of the identified risks to facilitate understanding.
4) Probable causes: This column identifies the root causes or triggering factors of the failure modes.
5) Potential effects: This column describes the consequences of each failure mode, in terms of direct or indirect impact on staff health, laboratory safety or analysis quality.
6) Frequency (before action): This column assesses the probability of occurrence of each risk on a scale from 1 (very rare) to 5 (very frequent).
7) Severity (before action): This column assesses the intensity of the negative impact of each failure mode, rated on a scale from 1 (negligible impact) to 5 (major/critical impact).
8) Detectability (before action): This column assesses the ability to detect a failure before it generates effects, with a scale from 1 (very easy to detect) to 5 (very difficult to detect).
9) Initial criticality: This column calculates the risk level by multiplying severity, frequency and detectability, thus making it possible to prioritize actions to be taken according to the formula $C = S \times F \times D$.
10) Action plan: This column proposes corrective and/or preventive measures to be implemented to reduce the criticality of the identified risks.
11) Responsible parties: This column establishes the persons responsible for each action to be implemented (the Quality Manager, Quality Control Specialist and Laboratory Analyst).
12) Frequency (after action): This column reassesses the probability of occurrence of the failure mode after the implementation of corrective measures.
13) Severity (after action): This column reassesses the potential impact of each failure mode, once corrective actions have been implemented.

14) Detectability (after action): This column reassesses the ability to detect failure modes after the implementation of action plans.

15) Residual criticality: This column calculates the criticality of the risk after the implementation of actions, thus indicating the effectiveness of the measures taken to control the risk, according to the formula C' = S' × F' × D'.

A risk assessment grid was developed and proposed, initially, within the quality control laboratory of CEVA *« Santé Animale »* Algeria. It was then the subject of a structured discussion with the relevant managers (quality manager and laboratory manager) as well as with the internship supervisor, before being formally validated and approved at the end of the process.

Table 8 : Risk Assessment Grid (1-to-5 Scale)

Criteria / Level (1 to 5 scale)	Severity (S)	Frequency (F)	Detectability (D)
5	Catastrophic	Very frequent	Impossible to detect
4	Critical (major)	Frequent	Very difficult to detect
3	Severe (moderate)	Probable	Moderately detectable
2	Minor	Rare	Easily detectable
1	Negligible	Very rare	Very easy to detect (obvious)

***Source**: adapted from El Kara et al. (2025) and IEC 31010:2019*

Criticality: C = S × F × D

This table presents a rating scale from 1 to 5 applied to the three fundamental dimensions of FMEA analysis: detectability, frequency (or probability) and severity. These three criteria are essential to the risk management process, as they successively structure the phases of identification, assessment, prioritization and treatment of failures within a system or process, and guide the definition of targeted preventive or corrective actions, in accordance with the requirements of ISO 31000:2018 and Good Manufacturing Practices (GMP).

Section 2: Organizational Framework

1. CEVA Santé Animale SPA: Company Overview and Organizational Structure

1.1 Company Presentation

CEVA *« Santé Animale »* SPA, established on 20 March 1999 as a wholly-owned subsidiary of the French group CEVA *«Santé Animale »* one of the world's top 5 animal health companies, is a key player in the Algerian veterinary pharmaceutical sector.

The company specializes in the local production of certain pharmaceutical forms (liquids and powders), complemented by the importation and distribution of finished veterinary medicinal products from the CEVA group.

Operating in a strictly regulated environment under the oversight of the Ministry of Agriculture and Rural Development (Directorate of Veterinary Services) and the Ministry of Pharmaceutical Industry, in coordination with local authorities, CEVA *« Santé Animale »* A plays a strategic role in supplying high-quality veterinary pharmaceuticals to the Algerian market. By ensuring the availability of effective solutions for livestock health, the company contributes significantly to improving animal productivity and supporting food security in Algeria.

1.2. Implantation in Algeria

The company is located in the pharmaceutical industrial zone of El Boustène, Rahmania, at Route de Douera, RN 63 - ZA El Boustène, Rahmania, Algiers (B.P. 76, 16301 Mahelma). This strategic site, situated in a developing industrial area dedicated to pharmaceutical and high-tech industries, supports efficient production, quality control, and distribution activities while facilitating full compliance with national regulatory and environmental requirements.

Legal and Administrative Information:

- Trade name: CEVA *« Santé Animale »* SPA
- Legal form : Société par Actions (SPA)
- Share capital: 241,269,287 Algerian Dinars
- Sector of activity (Branche d'activité): Veterinary pharmaceutical products
- Telephone: +213 (0) 23 07 73 25
- Fax: +213 (0) 23 07 73 21
- E-mail: cevaalgeria@ceva.com

1.3. Company Policy

CEVA has established a comprehensive Health, Safety and Environment (HSE) policy grounded in three foundational principles “One Ceva, One Health, One Planet” sustained by core corporate values encompassing passion for clients and animals, entrepreneurial spirit, innovation, and solidarity. Recognising that occupational health, workplace safety, and environmental protection constitute imperatives that demand a fundamental paradigm shift, the company has structured its HSE commitment around four strategic pillars.The Governance pillar encompasses the definition of HSE rules, the deployment of strategic objectives, the training of personnel to develop organisational competencies, and the continuous improvement of development and industrialisation processes. The Safety pillar focuses on the systematic detection and resolution of risk situations, the reduction of accident rates through targeted action plans, and the mitigation of site-specific operational risks. The Health pillar addresses the prevention of occupational diseases and professional illnesses, the integration of ergonomic principles from the earliest project phases, and the adaptation of workstations to accommodate employees' individual circumstances, including those affected by accidents or vulnerability. Finally, the Environment pillar is oriented towards reducing energy consumption, developing renewable energy sources, monitoring resource use including water and energy and achieving mastery over waste management practices. This policy is fully integrated into the group's Corporate Social Responsibility (CSR) framework and is operationalised through the 2023 HSE Roadmap, declined at each campus under the direct responsibility of HSE Managers, whose leadership and engagement are deemed essential to its effective implementation. As explicitly stated in the policy document, the successful execution of this approach requires the active involvement of all stakeholders across the organisation.

1.4 Product Range in Algeria

CEVA «*Santé Animale*» SPA offers a diversified and high-quality range of veterinary products adapted to the Algerian livestock sector, with a strong emphasis on poultry and ruminants, which represent the backbone of local animal production. The portfolio includes both locally manufactured items and imported specialties from the CEVA group.

Key categories include:

- Poultry: Vaccines against major diseases (Newcastle disease, Infectious Bronchitis, Gumboro disease, Coryza, etc.), pharmaceutical products, disinfectants, and vaccination equipment.

- Ruminants (cattle, sheep, goats): Antibiotic therapy, reproductive management products, vaccines, antiparasitics (including trypanocides and endectocides), metabolic correctors (anti-diarrheals and rehydration solutions), and injectable anti-infectives such as Tulaven (a tulathromycin-based product recently added for respiratory diseases in cattle and footrot in sheep).
- Swine: Antibiotic therapy, vaccines, and products supporting reproduction and digestive health.
- Companion Animals: Solutions in cardiology, dermatology, behavior, and locomotion (primarily imported range).
- Other Products: Broad-spectrum antiparasitics for large animals and metabolic correctors for ruminants and poultry.

Local production mainly covers liquid and powder pharmaceutical forms, enabling faster supply and better adaptation to market needs, while the company benefits from the group's global innovation in vaccines and specialty therapeutics. This comprehensive range plays an important role in enhancing animal health, improving livestock productivity, and supporting food security in Algeria.

1.5 Role of the Physicochemical Quality Control Laboratory within the Company

The physicochemical quality control laboratory occupies a central and strategic position within CEVA *«Santé Animale»* SPA. It is responsible for conducting all quality control analyses on raw materials, semi-finished products, and finished products. As an essential component of the company's integrated quality management system, the laboratory guarantees the quality, safety, and efficacy of veterinary medicinal products prior to their release on the market. It directly supports regulatory compliance, risk management, and the implementation of corrective and preventive actions (CAPA).

2. Presentation of the Physicochemical Quality Control Laboratory:

2.1 Type of Analyses

The laboratory specializes in physico-chemical analyses of veterinary pharmaceutical products. It performs systematic testing on raw materials, active pharmaceutical ingredients (APIs), semi-finished products, and finished dosage forms. Key analyses include identification and assay of active substances, purity tests, pH measurement, viscosity, moisture content, and stability studies. These tests ensure full compliance with product specifications and applicable standards.

(Microbiological analyses are conducted in coordination with the dedicated microbiology laboratory.)

2.2 Organisation of the Laboratory

The laboratory operates under the direct supervision of the Quality Manager and forms an integral part of the company's quality control unit. It is equipped with modern analytical instruments and functions according to strictly documented Standard Operating Procedures (SOPs). The team, composed of qualified technicians and analysts, works on an eight-hour shift basis. All activities are fully documented to ensure complete traceability, and the laboratory maintains close coordination with the two production lines (liquid and powder forms).

3. Importance in Quality Assurance

The physicochemical quality control laboratory is a cornerstone of CEVA *«Santé Animale»* SPA's quality management system. Through rigorous physico-chemical testing, it ensures that every batch meets the highest standards of quality, safety, and efficacy before release. The laboratory plays a critical preventive role in avoiding the distribution of non-compliant products, supports adherence to Good Manufacturing Practices (GMP), and actively contributes to the company's continuous improvement policy via internal audits and CAPA processes. Its activities are therefore fundamental to protecting animal health and preserving the company's reputation in the Algerian veterinary pharmaceutical market.

CHAPTER III: RESULTS AND DISCUSSION

This chapter constitutes the applied core of the present dissertation. It integrated and operationalised, in a coherent manner, the theoretical foundations developed in the preceding chapters within a real, documented context: the management of chemical risks associated with the handling of eight toxic substances in the physico-chemical quality control (QC) laboratory of CEVA Algeria.

The selection of CEVA Algeria as the field study site was justified by several determining factors. The company is a representative actor in the veterinary pharmaceutical industry in Algeria, subject to both national and international Good Manufacturing Practice (GMP) requirements. Its physico-chemical QC laboratory routinely handled a panel of eight substances exhibiting varying degrees of toxicity and risk, thereby offering a rich and representative field of investigation. The three-month on-site immersion affords sufficient depth to guarantee the validity and rigour of the data collected.

The methodology adopted followed the ISO 31000:2018 risk management process across five sequential and interlinked steps:

- Step 1 - Context establishment and initial diagnostic assessment via a GMP compliance checklist covering 41 criteria distributed across 8 chapters;
- Step 2 - Risk identification through qualitative triangulation of three complementary sources: direct observation, semi-structured interviews, and documentary analysis;
- Step 3 - Risk analysis using the FMECA method ($C = S \times F \times D$) applied to 12 scenarios across 8 substances;
- Step 4 - Risk evaluation using a criticality matrix and prioritisation of action items;
- Step 5 - Risk treatment and optimisation through a plan comprising 9 corrective and preventive actions, accompanied by performance indicators.

This chapter is structured in two sections: Section 1 presents the full results derived from the GMP compliance checklist, the interviews, the FMECA analysis, and the treatment plan; Section 2 presents the discussion and analytical review of results, the confrontation with the scientific literature, methodological limitations, and research perspectives.

Section 1: Data analysis

1. Context Establishment (ISO 31000 - Step 1)

In accordance with ISO 31000:2018, the risk management process began with the establishment of the internal and external context of the organisation. For the physico-chemical QC laboratory of CEVA Algeria, this context was defined as follows.

1.1 Scope and Objectives of the Study

The scope of the study encompassed the management of chemical risks associated with eight toxic substances routinely used in physico-chemical quality control analyses, particularly through HPLC, UV-Vis spectrophotometry, Karl Fischer titration, infrared spectrometry (IR), gravimetry, and titrimetry. The objective was to identify, analyse, and evaluate all chemical risks to which laboratory personnel are exposed, and subsequently to propose a prioritised treatment plan together with performance monitoring indicators.

1.2 Stakeholders (Internal and External)

The stakeholders identified within the framework of this study classified as internal and external are presented in the following table:

Table 9: Stakeholders of the Chemical Risk Management Study CEVA Algeria

Stakeholder	**Profile / Role**	**Interest in the Process**
Internal Stakeholders		
Senior Management	Responsible for resource allocation and chemical safety policy	Regulatory compliance; reduction of operational risks
Quality Control Manager (5 years' experience)	Supervises SOP compliance, risk management and CAPA	Continuous improvement of the QMS; control of non-conformities
Pharmaceutical Chemist-Analyst (8 year’s experience)	Direct daily handling of hazardous chemical substances	Reduction of personal exposure to chemical risks

QC Specialist (1 years' experience)	Supervision of analytical operations	Compliance of laboratory practices
HSE Manager	Management of PPE, chemical waste, and incident reporting	Environmental compliance and occupational safety
External Stakeholders		
Ministerial Inspectors (Directorate of Mines, Ministry of the Environment)	External regulatory inspectors	Verification of compliance with Algerian legal requirements

***Source**: compiled by the author based on field data - CEVA Algeria, 2026.*

1.3 FMECA Scoring Scales

The FMECA scoring scales were determined on the basis of the scientific literature and validated against the qualitative data collected in the field:

Table 10: FMECA Scoring Scales (F, S, D) and Criticality Thresholds

Parameter	**Level (1 → 5)**	**Description**
Frequency (F)	1:Very rare → 5: Near-certain	1: < once in 5 years 2: Annual 3: Monthly 4: Weekly 5: Daily/continuous
Severity (S)	1 : Negligible → 5 : Catastrophic	1: No injury 2: Minor injury 3: Reversible injury 4: Serious injury 5: Irreversible/fatal

Detectability (D)	1 Immediate → 5 Undetectable	1: Very easy to detect (obvious) 2: Easily detectable 3: Moderately detectable 4: Very difficult to detect 5: Impossible to detect
C = S × F × D	Criticality thresholds	C ≤ 10: Negligible C 11–25: Minor C 26–60: Moderate (priority action required) C 61–100: Critical C > 100: Catastrophic

Source: *adapted from* (El Kara, et al., 2025) *and* (IEC31010:2019), *validated against field data - CEVA Algeria, 2026.*

Methodological note: F, S, and D scores were determined through systematic triangulation of the three qualitative data sources: direct observation (3-month field immersion including five structured observation sessions), interviewee feedback, and SDS/SOP data. The scores were submitted for informal validation by the laboratory's QC Manager at the end of the internship. Criticality thresholds applied in this chapter follow the five-level scale defined in Chapter 2 (Section 2), adapted from (El Kara, et al., 2025)and (IEC31010:2019):

- Negligible (C ≤ 10),
- Minor (C 11–25),
- Moderate (C 26–60),
- Critical (C 61–100),
- Catastrophic (C > 100).

All CI classifications, priority zones, and corrective action urgency levels in this chapter are derived from this scale.

2. Initial Diagnostic Assessment: GMP/cGMP Evaluation Checklist

2.1 Evaluation Methodology

The GMP compliance checklist was conducted at the physico-chemical quality control laboratory of CEVA Algeria during a three-month field immersion, using a structured evaluation grid covering 8 chapters of Good Manufacturing Practice. The evaluation addressed 41 criteria distributed across the following domains: Quality System, Personnel, Premises and Equipment, Documentation, Laboratory Operations, Reagents and Chemical Substances, Chemical Waste Management, and PPE.

In accordance with the qualitative approach defined in Chapter 2, data collection relied on the triangulation of three complementary sources:

- Participant observation of laboratory practices over a 3-month field immersion.
- Semi-structured interviews with three key personnel: Pharmaceutical Chemist (8 years' experience), QC Manager (5 years), and QC Specialist (1 year).
- Documentary analysis of SOPs, SDS binders, training records, incident logs, and chemical risk registers.

Compliance was assessed according to three modalities: Yes (fully compliant), Partial (partially compliant counted as non-compliant in rate calculations), and No (non-compliant). Deviations were classified as Major (significant GMP deviation corrective action within 15 days) or Minor (isolated deviation corrective action within 3 months).

2.2 GMP Compliance Checklist - Chapter-by-Chapter Evaluation

The detailed GMP Compliance Checklist, evaluated on a chapter-by-chapter basis, is provided in full in Appendix A. The checklist encompasses all criteria assessed across each GMP chapter, with individual compliance determinations recorded therein.

2.3 Summary of the Overall Compliance Rate (% per GMP Chapter)

Following the completion of the GMP compliance checklist, the results were aggregated by chapter in order to determine the overall compliance rate per domain. These findings are presented in Table 11 below.

Table 11: Summary of GMP Compliance Rates by Chapter: CEVA Algeria

GMP Chapter	**Total Criteria**	**Compliant (Yes)**	**Compliance Rate**
Chapter 1 : Quality System	5	5	**100%**
Chapter 2 : Personnel	5	5	**100%**
Chapter 3 : Premises & Equipment	6	5	**83%**
Chapter 4 : Documentation	6	6	**100%**
Chapter 5 : Laboratory Operations	5	4	**80%**
Chapter 6 : Reagents & Chemical Substances	4	3	**75%**
Chapter 7 : Chemical Waste	5	2	**40%**
Chapter 8 : PPE	5	5	**100%**
OVERALL TOTAL	**41**	**35**	**85%**

Source: *compiled by the author*

The overall compliance rate of 85% reflects a laboratory with solid foundations in quality system management, personnel qualification, documentation, and PPE four domains achieving 100% compliance. Chapters 6 (75%) and 7 (40%) constitute the priority areas for intervention.

The poor performance in Chapter 7 is primarily attributable to a systemic technical constraint: the mixed composition of mobile phases (acid + organic solvent) renders categorical waste separation impossible under the current analytical setup. This situation does not reflect a lack of intent, but rather an infrastructural limitation inherent to the analytical methods employed. Chapter 6 is penalised by the impossibility of minimising quantities, as analytical protocols impose fixed, non-negotiable volumes defined by pharmacopoeial monographs.

3. Mapping of Priority Non-Conformities

Analysis of the GMP compliance checklist identified 11 non-conformities, of which 9 were classified as major. The most critical are detailed below, ranked by priority for intervention:

- Priority 1: Hazardous waste not separated by category (mixed mobile phases: acid + solvent): major non-conformity in Chapter 7 high impact action: separate labelled containers by category + written procedure within 15 days.
- Priority 2: Acids and bases stored in the same cabinets: major non-conformity in Chapter 3 risk of violent exothermic reaction action: dedicated separate storage cabinets for acids and bases within 15 days.
- Priority 3: Waste containers not separated by chemical category: major non-conformity in Chapter 7 action: implement category-labelled containers immediately.
- Priority 4: Toxic quantities not minimised: volumes imposed by analytical monographs action: review available packaging formats and implement just-in-time ordering.
- Priority 5: Spill response not formalised: instructions only, no written SOP action: draft spill response SOP and conduct practical drill within 1 month.
- Priority 6: Karl Fischer reagent used without dedicated fume cupboard or local ventilation: major non-conformity action: install local extraction at the KF workstation immediately.
- Priority 7: Methanol: absence of documented refresher training for certain analysts action: schedule refresher training within 15 days.
- Priority 8: Chronic VOC exposure underestimated (confirmed by all 3 interviewees) action: implement ambient air quality monitoring.
- Priority 9: Inadequate stoppers/closures causing vapour leaks (confirmed by all interviewees) action: replace inadequate closures; daily verification added to SOP checklist.

4. Summary of Semi-Structured Interviews

4.1 Interview Summary Table

The findings of the three semi-structured interviews are synthesised in Table 12 below, organised by thematic axis and cross-referenced across the three interviewee profiles in order to facilitate convergence analysis

Table 12: Summary of Semi-Structured Interview Results by Theme and Interviewee Profile-CEVA Algeria

Theme / **Axis**	**Chemist (8 years)**	**QC Manager (5 years)**	**QC Specialist (1 year)**
Profile	Direct daily handling of hazardous chemicals. Highly experienced.	Biologist-engineer focused on quality management; no direct handling.	Supervisory role; present in the laboratory during analyses.
Most hazardous substances	Methanol, isopropanol, acetonitrile high chronic risk.	Volatile organic solvents: acetonitrile, methanol, chloroform chronic exposure.	Same solvents confirmed continuous exposure via HPLC, UV-Vis, Karl Fischer.
Highest-exposure operations	Weighing, solution preparation, waste management concentrated exposure.	Inventory management and storage control systematic exposure.	Supervision of operations; regular presence during preparation.
Reported chemical incident	Toxic fume leak during sulfated ash analysis undersized plastic fume cupboard with low-capacity fan.	Same incident. Corrective actions: enhanced ventilation and periodic inspection.	Same incident confirmed. Systemic origin acknowledged.
Underestimated risks	Chronic VOC inhalation (methanol,	Chronic VOC exposure	Methanol, acetonitrile,

	acetonitrile) via continuously operating analytical equipment.	underestimated despite available SDS. No systematic monitoring.	isopropanol underestimated due to near-continuous exposure.
PPE adequacy	Appropriate PPE (panoramic mask with suitable filters). Systematic use.	PPE generally adequate; systematic use variable depending on individual discipline.	Appropriate PPE used systematically by analysts.
SOP accessibility	Clearly defined, available, and applied daily.	Well defined and accessible, but daily compliance not always optimal enhanced oversight required.	SOPs clearly defined, accessible, and applied.
Waste management	Managed in accordance with laboratory procedures; validated by Ministry of the Environment inspectors.	Procedures compliant with Ministry of the Environment requirements.	Procedures confirmed. Considered compliant.
Priority gaps / improvements	Inadequate stoppers/closures causing vapour leaks.	Same closure issue + insufficient fume cupboard maintenance. More frequent internal evaluations required.	Primary gap: stoppers causing vapour leaks. Improve fume cupboards and closures.

Source: *compiled by the author based on semi-structured interviews*

4.2 Interpretation of Results

Analysis of the three interviews reveals a strong convergence on priority risks, alongside perspective divergences attributable to the seniority level and role of each interviewee.

Major convergences:

All three interviewees independently and consistently identified two categories of risk that are systematically underestimated in daily practice and absent from standard GMP checklists:

- Chronic VOC inhalation via continuously operating analytical equipment (HPLC, UV-Vis, Karl Fischer): despite available Safety Data Sheets, no systematic ambient monitoring is in place, and near-continuous exposure to acetonitrile, methanol, and isopropanol is normalised in routine practice.
- Vapour leaks caused by inadequate stoppers and closures: all three interviewees, regardless of seniority or role, independently flagged this as the primary uncontrolled risk in daily operations a finding that does not appear in any regulatory GMP checklist, confirming the irreplaceable value of direct field observation and qualitative interviews in risk identification.

Documented major chemical incident:

The toxic fume release incident during sulfated ash analysis was reported independently by all three interviewees. This incident, caused by an initially undersized fume cupboard (plastic curtains, low-power fan), led to a complete overhaul of the extraction system (toughened glass, sliding door, high-power fan). It illustrates the relevance of a proactive approach: the most serious risks arise precisely where existing control measures were considered adequate.

Role-dependent divergences:

The Chemist (8 years) adopts an operational perspective focused on direct handling risks. The QC Manager (5 years) is the only participant to formally reference F × S (Frequency × Severity) risk matrix aligned with ISO 31000 methodology and to highlight gaps in daily SOP compliance. The QC Specialist (1 year) provided consistent but less in-depth responses in risk assessment, as would be expected for a supervisory role still developing in scope.

4. Chemical Risk Identification (ISO 31000 - Step 2)

4.1 Qualitative Sources for Risk Identification

In accordance with the qualitative approach defined in Chapter 2, risk identification was based on the systematic triangulation of three complementary data sources collected during the three-month field immersion at CEVA Algeria:

- Field diagnostic record: 8 chemical substances, analytical tasks, locations, PPE used, existing control measures, and a documented incident (sulfuric fumes);

- GMP compliance checklist grid: 41 criteria evaluated, 11 non-conformities identified and classified by chapter;
- Semi-structured interview summary: 3 interviewees data collected through direct observation, recorded interviews, and documentary analysis (SDS, SOPs, incident records).

Note: The GMP compliance checklist constituted the starting point for risk identification. The non-conformities identified feed directly into the chemical risk identification grid, in accordance with the integrated approach endorsed by the thesis supervisor.

4.2 Consolidated Register of the 12 Identified Risk Scenarios

Triangulation of the three data sources yielded the following consolidated register, comprising 12 chemical risk scenarios for the 8 substances under consideration:

- Scenario 1: Acetonitrile: chronic VOC inhalation (HPLC, benchtop).
- Scenario 2: Acetonitrile: skin/ocular contact (goggles not systematically worn).
- Scenario 3: Chloroform: acute inhalation during extraction.
- Scenario 4: Methanol: chronic inhalation + refresher training not documented;
- Scenario 5: Petroleum ether: inhalation + fire/explosion risk.
- Scenario 6: Sodium hydroxide: chemical burn (skin/ocular contact).
- Scenario 7: Sodium hydroxide: chemical reaction during storage (acids + bases together).
- Scenario 8: Isopropanol: chronic inhalation (IR and HPLC rinsing).
- Scenario 9: DMF: CMR Cat. 1B dermal absorption + inhalation.
- Scenario 10: Karl Fischer reagent: SO2/methanol inhalation without fume cupboard;
- Scenario 11: All volatile solvents: vapour leaks from inadequate closures (cross-cutting scenario).
- Scenario 12: All solvents/waste: mixing of hazardous waste in common containers.

5. Risk Analysis: FMECA (ISO 31000 - Step 3)

5.1 FMECA Methodology and Justification of Scores

The Failure Mode, Effects and Criticality Analysis (FMECA) was applied to each of the 8 chemical substances for their principal tasks and exposure scenarios. The FMECA table follows the 15-column structure defined in Chapter 2, Section 1.

Each F, S, and D score was determined through systematic triangulation of the three field data sources. The scores were submitted for informal validation by the laboratory's QC Manager at the close of the internship, strengthening their practical credibility without constituting formal validation in the metrological sense.

Two CI values are calculated per scenario: the Initial CI (current state, with existing control measures) and the Residual CI (projected state following corrective actions). This dual scoring enabled quantification of the risk reduction potential of each proposed intervention.

5.2 FMECA Table: 8 Substances × 12 Risk Scenarios

A full account of the FMECA results for the twelve identified scenarios is provided in Appendix C

5.3 Key Findings of the FMECA

The FMECA of the 12 risk scenarios yields the following key findings:

Five scenarios fall within the Moderate criticality zone (CI 26–60) and require priority corrective action without awaiting the next evaluation cycle:

• vapour leaks from inadequate closures (CI = 36),

• chronic acetonitrile inhalation (CI = 32),

• chronic methanol inhalation (CI = 32),

• DMF-CMR exposure (CI = 30),

• Petroleum ether inhalation/fire risk (CI = 30).

The Karl Fischer workstation represents the most critical engineering emergency: F = 5 (daily use without dedicated local extraction, confirmed by direct observation), S = 4 (SO2/methanol vapours, toxicity confirmed by SDS), CI = 20 engineering priority number one.

The 'vapour leaks from inadequate closures' scenario (CI = 36) is the most critical in the entire study and emerged exclusively from field interviews, confirming the irreplaceable value of a qualitative approach in identifying risks invisible to regulatory checklists.

Following implementation of corrective actions, the projected average CI reduction is 70.5%, with all residual CIs within the acceptable or tolerable range (CI ≤ 10), confirming the feasibility and effectiveness of the proposed treatment plan.

6. Risk Evaluation: Criticality Matrix (ISO 31000 - Step 4)

6.1 5×5 Criticality Matrix

The criticality matrix below graphically represented the position of each risk scenario along the Frequency (F) and Severity (S) axes.

Table 13: Risk Criticality Matrix the Frequency (F) vs. Severity (S) 12 Scenarios

S / F	1 Negligible	2 Minor	3 Moderate	4 High	5 Catastrophic
5 Near-certain	5	10	15	**20 Karl Fischer**	**25**
4 Probable	4	8	36 Closures	**32 Acetonitrile / Methanol**	20
3 Occasional	3	6	32Acetonitrile. Contact	24Chloroform / NaOH 24 Isopropanol	**30 Ether / DMF**
2 Unlikely	2	4	6	8	10
1 Very rare	1	2	3	4	5

Source: *compiled by the author.*

Legend: Red = Unacceptable (immediate action), Orange = High priority, Yellow = Tolerable, Green = Acceptable.

Note: the matrix positions scenarios according to F (Frequency) and S (Severity) axes. The final CI integrates Detectability (D) according to the formula CI = F × S × D; the CI values shown correspond to the full CI values from the FMECA table.

6.2 Classification of Scenarios by Risk Zone

MODERATE zone (CI 26–60) Priority corrective action required:

- Vapour leaks from inadequate closures (CI = 36),
- Acetonitrile chronic inhalation (CI = 32),
- Methanol: chronic inhalation (CI = 32),
- DMF: CMR exposure (CI = 30),
- Petroleum ether: fire/inhalation (CI = 30).

MINOR zone (CI 11–25) Planned corrective action (priority by CI magnitude):

- Karl Fischer SO2 inhalation (CI = 20)
- Mixed waste (CI = 16);
- Chloroform inhalation (CI = 24);
- NaOH chemical burn (CI = 24);
- Isopropanol: inhalation (CI = 24);
- Acetonitrile: ocular contact (CI = 18);
- NaOH: storage reaction (CI = 15).

NEGLIGIBLE zone (CI ≤ 10) Residual state after corrective actions:

No scenario falls within the negligible zone in the initial state. Following implementation of corrective actions, all residual CIs are projected to fall within the Negligible zone (maximum residual CI = 10).

6.3 Corrective Action Triggering Thresholds

- CI 26-60 (Moderate zone): priority corrective action within 15 days (GMP major non-conformity standard);
- CI 11-25 (Minor zone): planned corrective action priority sequenced by CI magnitude;
- CI ≤ 10 (Negligible zone): maintenance of existing measures review at next evaluation.

7. Risk Treatment and Optimisation Plan (ISO 31000 - Step 5)

7.1 Treatment Strategy

The treatment plan constitutes the CAPA (Corrective and Preventive Action) output of this study, as defined in Chapter 1, closing the risk management loop between FMECA findings and operational improvement. It followed the ISO 31000 control hierarchy:

Elimination > substitution > engineering controls > administrative controls > PPE.

The 9 actions are classified by type and sequenced according to the urgency of their initial CI values. This hierarchy ensured that the most robust solutions (engineering controls) are prioritised over behavioural solutions (training, procedures), in accordance with the principles of occupational risk prevention.

Table 14 Risk Treatment and Optimisation Plan: 9 Corrective and Preventive Actions

Ref.	**Corrective / Preventive Action**	**Type**	**Risk(s) Addressed**	**Deadline**	**Responsible Party**	**Indicator / KPI**
T1	Separate acid and base storage cabinets	Engineering control	Ch.3 / NaOH	**Immediate < 15 days**	HSE Manager	Zero chemical storage incidents
T2	Install local extraction at the Karl Fischer workstation	Engineering control	KF reagent	**Immediate < 15 days**	Maintenance + QC Manager	Air quality at KF workstation < OEL
T3	Replace all inadequate stoppers/closures	Engineering control	All volatile solvents	**Immediate < 15 days**	QC Manager + Analyst	Zero vapour leaks detected
T4	Implement ambient VOC air quality monitoring	Monitoring	All VOCs	Short term < 1 month	HSE Manager + External lab	VOCs < 50% of OEL
T5	Separate waste containers by chemical category	Procedural	Ch.7 / Waste	**Immediate < 15 days**	Analyst + HSE Manager	100% waste correctly categorised

T6	Draft formal spill response SOP + practical drill	Procedural	All substances	Short term < 1 month	QC Manager	SOP signed; drill documented
T7	Refresher training: methanol + CMR substances (DMF, chloroform)	Training	Methanol, DMF, Chloroform	Short term < 1 month	QC Manager + Trainer	100% analysts trained and assessed
T8	Replace nitrile gloves with butyl gloves for DMF	PPE optimisation	DMF (CMR Cat. 1B)	Short term < 1 month	HSE Manager	Zero dermal absorption of DMF
T9	Extend ventilation SOP to all volatile substance preparations	Procedural	Ch.5 / All	Short term < 1 month	QC Manager	SOP revised and signed

Source: *compiled by the author*

Priority: Red = Immediate (< 15 days) | Yellow = Short term (< 1 month).

7.2 SOPs to Draft or Revise

The treatment plan required the drafting or revision of the following standard operating procedures:

- SOP-CHM-01 (Revised): Handling of volatile organic solvents: mandatory fume cupboard closure during HPLC operation, container closure verification, revised PPE including replacement frequencies

- SOP-CHM-02 (Revised): Karl Fischer titration: mandatory local extraction, KF waste disposal procedure, specific SO2/methanol precautions
- SOP-WAT-01 (Revised): Chemical waste management: category separation table, mixed mobile phase protocol, chemical compatibility matrix
- SOP-EMG-01 (New): Spill and chemical burn response: step-by-step procedure, emergency contact list, post-incident documentation
- SOP-STR-01 (Revised): Chemical storage: mandatory acid/base cabinet separation with integrated compatibility matrix.

7.3 Training Programm

A structured five-module training programme was proposed to strengthen the chemical safety culture within the laboratory:

- Module 1: Chemical hazard identification: GHS/CLP pictograms, CMR classification, SDS reading (2 hours, annual);
- Module 2: Safe handling of specific substances: acetonitrile, methanol, chloroform, DMF focus on chronic exposure and glove permeation (2 hours, annual);
- Module 3: PPE use and limitations: nitrile glove permeation for chloroform/DMF, ABEK+P filter mask maintenance and replacement (1 hour, annual);
- Module 4: Emergency procedures: spill simulation, chemical burn first aid, evacuation protocol (practical drill, annual);
- Module 5: Waste management: category sorting, mixed mobile phase handling, waste register maintenance (1 hour, bi-annual).

7.4 Performance Indicators (KPIs)

Seven key performance indicators (KPIs) were proposed to monitor the implementation and effectiveness of the treatment plan:

Table 15: Key Performance Indicators (KPIs) for Monitoring the Treatment Plan

KPI Code	Designation	Description / Measurement	Target
KPI-01	Chemical incidents	Number of chemical incidents and near-misses per quarter	0 / year

KPI-02	GMP compliance	Overall GMP compliance rate per chapter	≥ 90% within 6 months
KPI-03	Residual CIs	% of risk scenarios with residual CI in the Negligible zone (CI ≤ 10)	100%
KPI-04	Training	% of analysts with up-to-date training records	100% at all times
KPI-05	Ambient air quality	VOC concentration / OEL for monitored substances	< 50% of OEL
KPI-06	Waste sorting	% of waste correctly separated by category at each disposal	100%
KPI-07	SDS currency	% of SDS up to date (< 5 years) and available in the working language	100%

Source: *compiled by the author*

These KPIs are to be measured during a follow-up evaluation at six months post-implementation, enabling verification of the effective reduction in CI values and adjustment of the action plan as necessary. They constitute the foundation of a continuous improvement system aligned with GMP requirements and ISO 31000.

Section 1 of this chapter presents the complete results arising from the integrated ISO 31000 + GMP/cGMP methodology applied to the physico-chemical quality control laboratory of CEVA Algeria.

The initial GMP compliance evaluation conducted during a three-month immersion covering 41 criteria distributed across 8 chapters established an overall compliance rate of 85%, with excellent performance in quality system management, personnel qualification, documentation, and PPE (100% each), alongside significant gaps in chemical waste management (40%) and reagent handling (75%). These deficiencies are partly attributable to structural constraints inherent to the analytical methods employed, which impose fixed mobile phase volumes and compositions that cannot be modified.

The synthesis of the three semi-structured interviews identified two categories of risk that are systematically underestimated and absent from regulatory checklists: chronic VOC inhalation

via continuously operating analytical equipment, and vapour leaks caused by inadequate closures the latter ultimately emerging as the most critical scenario in the entire study (CI = 36).

The FMECA of 12 risk scenarios across 8 toxic substances revealed that 5 scenarios (42%) fall within the Moderate criticality zone (CI 26–60), requiring priority corrective action. The nine-action treatment plan combining priority engineering controls, procedural revisions, targeted training, PPE optimisation, and ambient air quality monitoring is projected to reduce the mean CI by 70.5%, bringing all residual CIs within the Negligible zone ($C \leq 10$).

These results confirmed that the combined ISO 31000 + GMP/cGMP framework, applied within a rigorous qualitative approach involving data triangulation and extended field immersion (3 months), offers a more comprehensive and actionable diagnostic and decision-making tool than regulatory compliance assessment alone.

Section 2: Discussion of Results and Improvement Suggestions

1. Discussion of Results

Section 2 of this chapter carries out the interpretive and critical function that defines rigorous scientific work. Having presented in Section 1 the complete empirical results derived from the GMP compliance evaluation, the semi-structured interviews, the FMECA analysis, and the treatment plan, this section takes a step back to examine the meaning, scope, and limitations of those results. It confronts the findings with the existing scientific and regulatory literature, explicitly identifying convergence areas where the results confirm or reinforce established evidence and divergences areas where the present findings nuance, challenge, or extend prior knowledge. It then reflects critically on the methodological choices made and their implications, identifies the inherent limitations of this study, and outlines the research perspectives that this work opens. This dual analytical movement confrontation with the literature followed by methodological self-examination is necessary both to establish the scientific credibility of the results and to delineate the original contribution of this research, providing a direct and substantiated response to the central research question: whether the combined ISO 31000 + GMP/cGMP + FMECA framework constitutes an effective and contextually appropriate instrument for managing chemical risks in an Algerian veterinary pharmaceutical laboratory.

The confrontation of this study's findings with the existing scientific and regulatory literature reveals three major convergences. The first concerns the overall GMP compliance rate of 85%, which is entirely consistent with the 80–90% performance band documented in comparable pharmaceutical QC settings: comparable evaluations in pharmaceutical QC settings have documented compliance rates in the 80–90% range in laboratories with functional quality management systems (El Kara, et al., 2025); (Laarej, Jbilou, Bouatia, Elyadini, & Alami, 2021)), and the WHO GMP guidelines (World Health Organization, 2024) establish benchmark requirements against which this rate reflects an intermediate-to-high maturity level. CEVA Algeria therefore sits within a performance band that is both credible and representative of companies at an intermediate stage of their quality journey. The second convergence concerns the identification of chronic VOC inhalation as the highest-criticality scenario in the entire FMECA (CI = 36), a finding that is entirely consistent with, and significantly supported by, the occupational health and industrial hygiene literature. Chronic low-level exposure to VOCs such as acetonitrile, methanol, chloroform, and isopropanol in analytical laboratory environments has been repeatedly documented as a major occupational hazard, particularly in the context of continuously operating analytical equipment (HPLC, UV-Vis, Karl Fischer titration) whose

mobile phase consumption generates persistent, diffuse emission sources. (Bevilacqua, et al., 2023) documented that uncontrolled occupational exposure to solvents in pharmaceutical analytical laboratories can result in acute intoxication, chronic organ damage, and long-term carcinogenic effects; the Occupational Safety and Health Administration (OSHA, 2012) established occupational exposure limits specifically recognising the cumulative toxicity risks of solvents such as acetonitrile and methanol under conditions of daily analytical use; and INRS guidance documents further confirm that diffuse VOC emissions from continuously operating HPLC systems represent a priority occupational hygiene concern in analytical chemistry settings. The third convergence concerns the practical value of the combined ISO 31000 + GMP/cGMP framework. (Vukašinović, Obradović, & Debeljak, 2011), (Poli, Esposito, Aloj, & Lastoria, 2024), and (Dzen, 2026) all demonstrate that the structured iterative process of ISO 31000 adds analytical depth and prioritisation capacity that static GMP compliance evaluations alone cannot provide a finding directly supported by the results of the present study, where the ISO 31000 framework transformed a compliance rate and a list of non-conformities into scored, prioritised, residual-CI-tracked risk scenarios with assigned corrective actions, deadlines, responsible parties, and performance indicators.

Three significant divergences equally emerge from this confrontation. The first and most analytically original is the distinction between correctable organisational non-conformities and structurally constrained non-conformities that are inseparable from validated analytical methodology itself. The non-conformities in chemical waste management (40%) and reagent handling (75%) are not uniformly correctable: the impossibility of minimising toxic reagent quantities imposed by pharmacopoeial monographs, and the inseparability of mixed halogenated and non-halogenated mobile phases in waste streams dictated by HPLC analytical chemistry, constitute constraints that no procedural or engineering intervention can eliminate. Standard GMP evaluation frameworks treat all non-conformities as correctable; the present findings demonstrate that this conflation misrepresents the nature of compliance challenges in analytical chemistry settings, and that the ISO 31000:2018 principle of risk criteria adaptation (Clause 6.3) must be actively applied to differentiate genuine safety gaps from unavoidable by-products of validated analytical methods. This distinction is rarely made explicit in the existing pharmaceutical quality literature and constitutes an original analytical contribution of this study. The second divergence concerns the implementation of ISO 31000 itself. (Lalonde & Boiral, 2012a) argued that the standard’s non-prescriptive character limits consistent implementation across organisations; the present study demonstrates that, when operationalised

through a structured qualitative triangulation design combining extended field immersion, multi-seniority semi-structured interviews, and documentary analysis, the standard generates highly consistent and internally coherent risk prioritisation outputs suggesting that the implementation limitation identified by Lalonde and Boiral is more a function of methodological rigour than of the standard itself. Third, and most consequentially, the highest-criticality risk identified in this study chronic vapour exposure from inadequate container closures (CI = 36) was completely invisible to all compliant documentary instruments: the GMP checklist, the SDS system, and the chemical risk register were all rated as fully compliant. This finding diverges from the implicit assumption of most regulatory and risk assessment frameworks that documentary compliance provides adequate risk visibility, and illustrates with unusual clarity the epistemological limitation of purely documentary risk assessment.

The GMP evaluation results warrant more detailed analytical treatment. The two chapters with the lowest compliance scores chemical waste management (Chapter 7, 40%) and reagent handling (Chapter 6, 75%) exhibit the structural duality described above. The first category of non-conformity, represented by the acid/base co-storage gap (Chapter 3) and the incomplete spill response SOP (Chapter 7), reflects correctable organisational failures amenable to straightforward engineering and procedural interventions within the 15-day corrective action window. The second and more analytically significant category the impossibility of minimising toxic reagent volumes prescribed by pharmacopoeial monographs and the inseparability of mixed HPLC mobile phases in waste streams represents constraints imposed by validated analytical chemistry that cannot be resolved by procedural revision. This nuance strengthens the practical relevance of the evaluation findings for laboratory managers who must allocate remediation resources efficiently and avoid investing corrective action resources in structurally immovable constraints. The ISO 31000:2018 standard acknowledges precisely this type of situation through Clause 6.3, which permits adaptation of risk criteria to the specific operational context, thereby enabling a differentiated and honest treatment of the compliance landscape rather than a binary compliant/non-compliant judgement that would misrepresent both the severity and the correctable fraction of the identified gaps.

The finding that the highest-CI scenario of the entire study chronic diffuse VOC inhalation from inadequate container closures (CI = 36) was identified exclusively through qualitative field interviews and direct observation rather than through any documentary instrument deserves particular analytical attention, as it constitutes simultaneously the most significant methodological result and the most practically urgent safety finding of this dissertation. All

three interviewees, independently and without prompting, converged on inadequate container closures as the primary source of chronic vapour exposure in the laboratory. This convergence constitutes a robust qualitative finding in the sense defined by (Yin, 2018): independent corroboration from multiple data sources with no shared informational basis. The GMP compliance checklist, the SDS system, and the chemical risk register all rated as fully compliant were collectively incapable of surfacing this risk because it operates through a mechanism gradual degradation of container seals generating diffuse, sub-threshold, chronic vapour release that is invisible to compliance verification instruments designed to check the existence of documents, equipment, and procedures rather than to detect latent operational hazards. This result has direct and generalisable implications for the design of chemical risk management systems in pharmaceutical analytical laboratories: regulatory compliance documentation, however thorough and current, cannot substitute for systematic qualitative inquiry into the tacit, experiential knowledge of practitioners. The inclusion of semi-structured interviews with multi-seniority personnel in the risk identification process is not merely a methodological preference it is, on the evidence of this study, a functional necessity for identifying the most operationally significant chemical risks.

The identification of N,N-Dimethylformamide (DMF) as a Category 1B CMR substance for reproductive toxicity under REACH Regulation EC 1907/2006 and CLP Regulation EC 1272/2008, yielding a CI of 30 and placing it in the Moderate criticality zone, highlights a structural gap in PPE selection practices that is particularly prevalent in pharmaceutical QC laboratories operating under general laboratory norms rather than substance-specific risk evidence. The current use of nitrile gloves as the primary dermal barrier for DMF handling is directly contradicted by the glove permeation literature: Multiple studies on glove permeation have documented the inadequacy of nitrile gloves for DMF, with breakthrough times substantially shorter than a full work shift, and confirmed that butyl rubber provides significantly superior chemical resistance for polar organic solvents a finding consistent with the occupational safety guidance reviewed in this study ((Occupational Safety and Health Administration, 2012); (INRS, 2016); (IEC31010:2019)). Butyl rubber gloves, which offer a permeation resistance exceeding 480 minutes for DMF under standard conditions, represent the unambiguous evidence-based alternative. This situation also highlights a regulatory gap present in the Algerian framework (Executive Decree 91-05, 1991); (Executive Decree n° 05-09 8 january 2005): while the legislation requires PPE to be adapted to specific risks, it does not specify glove permeation criteria at the substance level, meaning that the responsibility for

evidence-based PPE selection falls entirely on the HSE manager and QC laboratory, without external verification. The corrective action T8 (replacement of nitrile with butyl gloves for DMF) therefore addresses both an immediate occupational health risk and a systemic gap in the laboratory's substance-specific risk management culture.

The combined ISO 31000 + GMP/cGMP framework applied in this study represents a deliberate methodological choice whose value and inherent tensions merit critical examination. ISO 31000:2018 is a generic, principle-based risk management framework that provides no prescriptive evaluation tools or substance-specific risk matrices; GMP/cGMP frameworks, by contrast, are highly prescriptive regulatory instruments focused on product quality assurance rather than occupational health risk. Their combination is therefore not a natural methodological pairing it is an engineered integration that required explicit justification and careful operationalisation. The principal contribution of ISO 31000 in this context is its provision of a structured, iterative five-step process context, identification, analysis, evaluation, treatment that imposes coherence on a field investigation that would otherwise risk remaining fragmented. Without this framework, the GMP checklist yields a compliance rate and a list of non-conformities: useful, but static, and incapable by itself of generating a prioritised, actionable, and monitored risk management plan. A genuine tension exists between the two frameworks at the level of risk acceptability criteria: GMP requirements are binary a criterion is either compliant or non-compliant, and a major deviation triggers a mandatory corrective action within 15 days regardless of underlying risk level while ISO 31000 is explicitly criteria-adaptive, permitting the organisation to define its own risk thresholds and prioritise actions according to CI magnitude. In this study, this tension was resolved pragmatically: the GMP binary classification informed the urgency of corrective actions while the CI scores informed their sequencing and depth. This pragmatic integration appears well-suited to the pharmaceutical QC laboratory context, but it introduces an element of methodological hybridity that should be acknowledged as a characteristic of this approach and not treated as a shortcoming.

The FMECA method (sec) was selected on the basis of its widespread validation in pharmaceutical quality and occupational risk management, its conceptual tractability in a qualitative data context, and its capacity to integrate the detectability dimension absent from simpler frequency×severity matrices a dimension that is particularly relevant in an analytical laboratory context where many chronic exposure scenarios are inherently difficult to detect without instrumental monitoring. The scoring validity of the FMECA in this study rests on two

complementary pillars: the triangulation of three independent field data sources for each F, S, and D score, and the informal validation of scores by the QC Manager at the close of the internship. These mechanisms are appropriate for a qualitative dissertation study, but they do not constitute formal metrological validation in the sense required for regulatory submission; the scores should therefore be understood as expert-informed qualitative estimates with demonstrated internal consistency rather than objectively measurable quantities. A comparison with alternative methods is instructive in contextualising this choice. The (OHSAS 18001, 2007)/ (ISO 45001:2018) occupational risk matrix (5×5 F×S, without a detectability dimension) would have yielded a simpler but less discriminating risk profile, conflating scenarios with similar probability and severity values but very different detectability characteristics. The Bow-Tie method, increasingly used in process industries, would have enabled more granular analysis of causal chains and barriers but requires substantially more data than was available from a three-month qualitative study. The FMECA therefore represents a well-calibrated choice for this context: sufficiently rigorous to generate actionable priorities, and sufficiently tractable to be applied systematically within the constraints of a qualitative dissertation study.

2. Limitations and Improvement Suggestions

This study is subject to four inherent limitations that must be acknowledged in interpreting its findings. The most fundamental is its single-site, single-laboratory case study design: in accordance with (Yin, 2018), the findings offer analytical generalisation informing methodological frameworks and theoretical propositions rather than statistical generalisation across a population of comparable laboratories, and their value resides accordingly in the rigour of the approach demonstrated and the principles it derives, not in the prevalence of specific risk scenarios. The bounded three-month observational window, while considerably more extensive than a standard evaluation visit, captures only a temporal cross-section of laboratory operations: given that chemical risk profiles evolve continuously with changes in analytical method portfolios, supplier transitions, personnel turnover, and seasonal variations in reagent use, the CI values reported herein may not fully reflect risks associated with less frequently performed analyses, and the projected residual CIs assume sustained implementation and stable operational conditions, underscoring the methodological necessity of the six-month follow-up evaluation stipulated in Section 3.8.4. Furthermore, the FMECA scoring of F, S, and D was conducted by a single researcher and subjected only to informal validation by one QC Manager, in the absence of a formal inter-rater reliability protocol; while this constraint is structurally unavoidable within the scope of a dissertation study and does not invalidate the results, future

investigations intended to inform regulatory or certification decisions should incorporate formalised inter-rater procedures such as Cohen's kappa. Finally, the scope of this study is expressly confined to the physico-chemical QC laboratory; the chemical risk profiles of other operational areas of CEVA Algeria pharmaceutical production, microbiological quality control, warehousing and logistics lie beyond its remit and should be addressed in subsequent assessments.

The findings of this study open several substantive avenues for future research. Most immediately, the combined ISO 31000 + GMP/cGMP + FMECA framework warrants application and comparative validation across other pharmaceutical QC laboratories in Algeria and the MENA region, with a view to distinguishing context-invariant risk patterns such as chronic VOC inhalation from continuously operating analytical equipment from site-specific ones, and to providing the multi-site evidential base required for broader analytical generalisation. From a technical standpoint, the most significant methodological development would be the integration of real-time quantitative ambient air quality monitoring employing VOC analysers, photoionisation detectors, and SO_2 electrochemical sensors into the risk assessment cycle, grounding the qualitative F and S estimates in instrumentally measured exposure data and enabling rigorous empirical verification of KPI-05 targets. The persistent gap between documented SOP requirements and observed daily practice attributable to risk habituation, normalisation of deviance, and the ergonomic constraints of sustained analytical work rather than to any absence of procedures or PPE points to a need for future research integrating safety climate measurement instruments with the ISO 31000 + FMECA framework, to produce a more complete explanatory model of behavioural non-compliance and enable more effective interventions. Finally, at the regulatory level, the friction points identified between Algerian occupational health legislation (Law n° 88-07), (Executive Decree 91-05, 1991), and international frameworks ISO 31000:2018, REACH, CLP particularly the absence of substance-specific occupational exposure limits for numerous laboratory solvents, call for systematic regulatory mapping research to support harmonisation efforts aligned with Algeria's pharmaceutical sector development strategy.

Taken together, the analyses developed in this section provide a direct and substantiated response to the central research question of this dissertation. The combined ISO 31000 + GMP/cGMP + FMECA framework constitutes an effective and contextually appropriate instrument for managing chemical risks in the physico-chemical QC laboratory of an Algerian veterinary pharmaceutical company, and its effectiveness derives from a specific mechanism:

the qualitative triangulation methodology creates the conditions for practitioners to make tacit knowledge explicit, surfacing risks that no documentary compliance instrument can detect. The convergences with the literature establish that the results are scientifically credible and methodologically generalisable; the divergences establish that they are empirically original and contextually situated. Both dimensions are necessary for a contribution that is simultaneously scientifically grounded and practically relevant.

Chapter 3 thus demonstrates, through a complete and critically examined field investigation, that the invisible risk vapour leaks from inadequate container closures, identified only through practitioner interviews yielded the highest criticality index in the entire study: a result that is both a methodological argument and a practical warning. In a well-documented laboratory, the most dangerous risks may be precisely those that no document records.

GENERAL CONCLUSION

This dissertation set out to answer the following question: How can risk management practices for toxic chemical substances in the physico-chemical laboratory of a veterinary pharmaceutical company be systematically optimized and assessed by integrating ISO 31000 and GMP requirements within a resource-constrained Algerian context? The empirical investigation conducted at CEVA Algeria over a three-month field immersion demonstrates that this objective has been fully achieved through the application of a combined ISO 31000 + GMP/cGMP + FMECA framework, implemented within a rigorous qualitative methodology grounded in multi-source data triangulation.

The GMP compliance evaluation covering 41 criteria across 8 chapters established an overall compliance rate of 85%, with four chapters achieving full compliance. The qualitative triangulation of direct observation, semi-structured interviews with three key personnel, and documentary analysis enabled the identification of 12 chemical risk scenarios across 8 toxic substances. The FMECA method, applied systematically to each scenario, yielded a complete criticality profile: five scenarios fall within the Moderate zone (CI 26–60) requiring priority corrective action vapour leaks from inadequate closures (CI = 36), chronic acetonitrile inhalation (CI = 32), chronic methanol inhalation (CI = 32), DMF-CMR exposure (CI = 30), and petroleum ether fire and inhalation risk (CI = 30). The root causes of these five priority scenarios were identified with precision: in each case, the causal mechanism is not the absence of a procedure but the gap between what documented procedures prescribe and what field practice produces a pattern that confirms the central argument of this work. The nine-action corrective and preventive treatment plan, combining engineering controls, procedural revisions, targeted training, PPE optimisation, and ambient air quality monitoring, is projected to reduce the mean criticality index by 70.5%, bringing all residual CIs within the Negligible zone ($CI \leq 10$).

Thus, this dissertation responds fully to its central research question and to both subordinate inquiries. The combined framework generates a demonstrably more comprehensive diagnostic than regulatory compliance assessment alone: the highest-CI scenario of the entire study chronic vapour exposure from inadequate container closures was completely invisible to all compliant documentary instruments, including the GMP checklist, the SDS system, and the chemical risk register. It was identified exclusively through practitioner interviews and direct observation, confirming that qualitative triangulation is not only capable of surfacing risks invisible to standard compliance instruments but is, in this context, functionally indispensable. The recommendations formulated are deliberately concrete and operational, taking into account

the resource and regulatory constraints of the Algerian pharmaceutical context while ensuring effective control of the identified risks.

Nevertheless, this study is subject to inherent limitations that must be acknowledged. The single-site case study design precludes statistical generalisation to other laboratories or national contexts; the three-month observation window captures only a bounded temporal cross-section of a dynamic risk environment; the FMECA scoring, while grounded in systematic triangulation and validated by the QC Manager, rests on expert-informed estimates rather than metrologically validated quantities; and the scope is expressly confined to the physico-chemical QC laboratory, excluding other operational areas of CEVA Algeria.

Looking ahead, several research perspectives emerge from this work. The combined ISO 31000 + GMP/cGMP + FMECA framework warrants application and comparative validation across other pharmaceutical QC laboratories in Algeria and the MENA region. The integration of real-time quantitative ambient air quality monitoring VOC analysers, photoionisation detectors, SO2 electrochemical sensors would ground the qualitative estimates in instrumentally measured exposure data and enable rigorous empirical verification of the KPIs proposed in this study. At the regulatory level, the friction points identified between Algerian occupational health legislation and international frameworks call for systematic regulatory mapping to support harmonisation efforts. Finally, the persistent gap between documented procedures and observed daily practice attributable to risk habituation and the ergonomic constraints of sustained analytical work points to a need for future research integrating safety climate measurement with the risk management framework. Ultimately, the rigorous and continuous application of the risk management approach developed in this dissertation will contribute to strengthening the chemical safety culture at CEVA Algeria, consolidating its regulatory compliance, and positioning it as a reference for sound occupational risk management practices in the Algerian veterinary pharmaceutical sector.

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APPENDICES

APPENDIX A: GMP Compliance Checklist

	GMP Compliance Checklist			Information sheet Version N :03 Elaborate by: Celina Magraoui
GMP Criterion	**Description**	**Compliance**	**Classification**	**Observations / Findings**
Chapter 1 - Quality System / Compliance rate: 100%				
Chemical risk policy	Policy defined and signed by management	Yes	/	Policy signed by management and in force.
Chemical safety responsibilities	Formally assigned to the HSE department	Yes	/	Monthly HSE committee formally designated.
Chemical risk register	Register up to date and audited	Yes	/	Register signed by Ministry; audited 4×/year.
Documented incidents	Incident log maintained	Yes	/	Sulfuric fume incident documented.
Management reviews	Periodic reviews conducted	Yes	/	12 meetings/year exceeds GMP requirement.
Chapter 2 - Personnel / Compliance rate: 100%				
Chemical risk training	Specific training delivered	Yes	/	Training provided at recruitment for all analysts.
Documented and renewed training	Renewed and assessed	Yes	/	Every 3 years or following CAPA. Records maintained.
Emergency procedures known	Evacuation plan posted	Yes	/	Annual simulation conducted.
SDS available and communicated	Information on toxic substances	Yes	/	SDS + pictograms; supplementary Ministry training.
Qualification programme	Role-specific authorisation for risk positions	Yes	/	Authorisation status defined per analyst.
Chapter 3 - Premises & Equipment / Compliance rate: 83%				
Fume cupboards	Compliant and tested annually	Yes	/	HVAC system. Qualified by accredited body. Upgraded following incident.
Flammable solvent storage	Secured DTD safety cabinets	Yes	/	Integrated toxic vapour extraction.
Acids/bases separation	Mandatory separate storage	**No**	**Major**	Acids and bases stored in THE SAME cabinets risk of violent exothermic reaction.
Chemical-resistant surfaces	Antibacterial resin benchtops	Yes	/	Throughout the laboratory.
Accessible safety showers/eyewash stations	Safety equipment present	Yes	/	Eyewash station and safety shower accessible.
Extractors tested annually	External accredited body	Yes	/	Tested annually.
Chapter 4 - Documentation / Compliance rate: 100%				
Current and accessible SDS	Updated at each purchase	Yes	/	PDF files and printed binders.
SOPs for hazardous substances	SOPs for all 8 substances available	Yes	/	Accessible in binders and on the QC server.
Waste and emergency SOPs	Procedures in place	Yes	/	Management and emergency procedures available.
Chemical records	Maintained and up to date	Yes	/	Chemical substance register maintained.
Training traceability	Training register with schedule	Yes	/	Renewal planned.

Annual SDS review	Cycle supervised by QC Manager	Yes	/	Revised upon supplier change.
Chapter 5 - Laboratory Operations / Compliance rate: 80%				
Weighing of toxics under fume cupboard	Handling with appropriate PPE	Yes	/	Observed and respected.
Preparation under ventilation	Systematic application	Partial	Minor	Under fume cupboard for the majority; ventilation not always applied for non-spray substances.
Spill-free transfers	Procedures respected	Yes	/	Transfer procedures followed.
Cleaning of contaminated glassware	Dedicated washing baths	Yes	/	Dedicated washing area.
Complete secondary labelling	All containers labelled	Yes	/	Compliant.
Chapter 6 - Reagents & Chemical Substances / Compliance rate: 75%				
Expired reagents removed	Disposal via HSE transfer form	Yes	/	Forwarded to incineration.
Storage by compatibility	Halogenated/non-halogenated solvents separated	Yes	/	Oxidising agents also separated.
Minimisation of toxic quantities	Fixed volumes required by protocols	**No**	**Major**	Quantities cannot be minimised pharmacopoeial monographs impose non-negotiable volumes. Increased chronic exposure.
CMR inventory up to date	Register controlled by Directorate of Mines	Yes	/	Electronic file updated quarterly.
Chapter 7 - Chemical Waste / Compliance rate: 40%				
Written disposal procedure	HSE co-managed procedure	Yes	/	Co-managed by analyst and HSE Manager.
Appropriate and labelled containers	Separation by category	**No**	**Major**	Containers not separated by chemical waste category.
Hazardous waste separated	Halogenated/non-halogenated distinct	**No**	**Major**	Mixed mobile phases (acid + solvent) cannot be separated under current conditions.
Waste monitoring register	Transfer form and register maintained	Yes	/	Documented tracking.
Spill response training	Instructions but no formal SOP	Partial	**Major**	Incomplete training on spill response.
Chapter 8 - PPE / Compliance rate: 100%				
PPE adapted to SDS requirements	Nitrile gloves, goggles, ABEK+P mask	Yes	/	All appropriate per SDS.
Systematic PPE use	Mandatory per HSE/PPL procedures	Yes	/	PPE systematically worn.
PPE inspected and replaced	Upon deterioration	Yes	/	Periodic replacement ensured.
PPE use training	Training at recruitment	Yes	/	Training provided at recruitment.
Emergency equipment	First-aid kit and functional eyewash	Yes	/	Accessible and maintained.

Source: *compiled by the author.*

Legend: Yes = compliant, Partial = partially compliant, No = non-compliant

Major = action required < 15 days, Minor = action required < 3

APPENDIX B: Interview guide

INTERVIEW GUIDE

Chemical Risk Management in the Physico-Chemical Quality Control Laboratory

GENERAL OBJECTIVE

This interview guide is designed to collect the perceptions and practical knowledge of physico-chemical quality control laboratory personnel regarding the risks associated with toxic and hazardous chemical products.

The data collected will serve to inform the situational diagnosis, identify existing risks, assess the adequacy of current control measures, and propose improvement actions within the framework of risk management in accordance with ISO 31000 and the requirements of Good Manufacturing Practices (GMP).

Specific Objectives:

- To identify the toxic chemical products present in the laboratory and the associated occupational exposures.
- To assess the likelihood and severity of chemical risks as perceived by laboratory personnel.
- To evaluate the level of compliance with GMP requirements regarding chemical safety.
- To identify gaps in prevention measures and prioritize improvement needs.

AXIS 01 - Professional Profile and Initial Training

N°	Question
Q1	What is your current position, educational qualification, year of recruitment, and how long have you been working in this laboratory?
Q2	What are your primary daily tasks involving the handling of chemical products?
Q3	Please describe the specific chemical safety training you have received since joining this position (content, frequency, duration, and concrete impact on your professional practices).

AXIS 02 - Identification and Assessment of Chemical Risks

- **Identification of Chemical Products and Exposure Situations**

N°	Question
Q4	Are you familiar with the hazardous products or hazard classifications present in the laboratory? Which chemical products do you handle most frequently (solvents, acids, bases, oxidizing reagents, toxic reagents, etc.)? Among these, which do you consider most hazardous and for what reasons?
Q5	During which operations do you feel most exposed to chemical risk (weighing, solution preparation, transfer, glassware cleaning, waste disposal, etc.)?
Q6	Can you describe in detail a chemical incident or near-miss that you encountered in this laboratory? (Context, triggering factors, incident management, and observed impacts.)

- **Assessment of Perceived Frequency and Severity**

N°	Question
Q7	For the principal chemical risks identified, how would you evaluate the frequency of occurrence and the severity of potential consequences? (Please use the rating scale provided in the appendix.)
Q8	Based on your professional experience, which chemical risks do you believe are underestimated or insufficiently addressed in the laboratory? Please elaborate on the situations concerned, the explanatory factors, and the potential impacts.

AXIS 03 - Chemical Risk Management and GMP Compliance

- **Prevention and Protection Measures in Place**

N°	Question
Q9	Are the personal protective equipment (PPE) provided appropriate for the chemical products you handle? Are they used systematically? If not, what are the reasons?
Q10	Are the standard operating procedures (SOPs) for handling hazardous chemical products clearly established, readily accessible, and consistently adhered to in daily practice?

N°	Question
Q11	How are chemical wastes managed within the laboratory (collection, labeling, storage, and disposal)? Do the existing procedures appear to comply with GMP requirements and are they considered adequate?

N°	Question
Q12	Please describe the conditions of access to Safety Data Sheets (SDS) in your laboratory: availability, frequency of updates, accessibility (paper/digital), language, and any limitations observed.
Q13	In your professional opinion, what are the primary deficiencies in chemical safety within this laboratory, and which improvements should be prioritized?

APPENDIX C: FMECA Matrix

Toxic Substance	Failure Mode	Risk Description	Probable Causes	Potential Effects	F	S	D	C	Action Plan	Responsible Party	F'	S '	D'	C'
Acetonitrile	Chronic inhalation during HPLC	Continuous VOC inhalation via HPLC mobile phase evaporation daily exposure	Continuous HPLC operation without systematic fume cupboard closure; absence of real-time VOC monitoring; inadequate re-capping	Chronic neurotoxicity; CNS impairment; long-term liver and kidney damage	4	4	2	**32**	Ambient VOC air monitoring; systematic fume cupboard closure during HPLC; immediate re-capping of containers	**Quality Manager + Laboratory Analyst**	2	2	2	**8**
Acetonitrile	Skin/ocular contact during prep.	Goggles not systematically worn during mobile phase preparation	Absence of mandatory goggles enforcement in SOP checklist; individual compliance variability	Ocular irritation and chemical burns; dermal sensitisation	3	3	2	**18**	Mandatory safety goggles protocol; goggles compliance added to daily SOP checklist	**Quality Manager**	2	1	3	**6**
Chloroform	Acute inhalation during extraction	Hepatotoxic vapour inhalation during mobile phase prep. and liquid-liquid extraction	Inadequate fume cupboard verification before use; nitrile gloves insufficient for chloroform permeation (short breakthrough time)	Acute hepatotoxicity; CNS depression; IARC Group 2A carcinogenic risk	3	4	2	**24**	Mandatory fume cupboard integrity check before each use; replace with butyl gloves for chloroform	**Quality Manager + Laboratory Analyst**	2	2	2	**8**
Methanol	Chronic inhalation + undocumented training	Chronic neurotoxic inhalation via HPLC; refresher training not documented for all analysts	Continuous HPLC use without systematic container re-capping; training renewal gap identified by Quality Control Manager	Optic nerve damage; metabolic acidosis; CNS effects; blindness at high doses	4	4	2	**32**	Mandatory refresher training for all analysts; ambient air VOC monitoring; systematic re-capping protocol	**Quality Manager**	2	2	2	**8**
Petroleum Ether	Inhalation +	Highly flammable vapour	Flash point below ambient temperature; ignition sources not	Flash fire or explosion; acute CNS inhalation	3	5	2	**30**	Eliminate all ignition sources near extraction bench;	**Laboratory Analyst + Quality Manager**	2	5	1	**10**

	fire/explosion risk	inhalation and ignition risk during extraction operations	systematically eliminated near extraction bench	toxicity; thermal burns					accessible fire extinguisher confirmed; minimise open-air exposure time					
Sodium Hydroxide	Chemical burn during pH adjust./titration	Skin and ocular contact with concentrated NaOH solution during preparation and titration	Handling without face shield; proximity to acid storage increases risk of accidental exothermic contact	Severe chemical burns to skin and eyes; permanent ocular injury; upper airway irritation	3	4	2	**24**	IMMEDIATE separation of acid/base storage cabinets; face shield mandatory for concentrated NaOH; eyewash station confirmed accessible	**Quality Manager + Laboratory Analyst**	2	2	2	**8**
Sodium Hydroxide	Violent reaction acid/base co-storage	Acids and bases stored in same cabinet risk of exothermic reaction (major non-conformity Ch.3)	Insufficient dedicated storage space; no acid/base separation protocol enforced; absence of chemical compatibility matrix in storage area	Violent exothermic reaction; toxic gas release; fire risk; severe personnel burns	3	5	1	**15**	Immediate installation of dedicated acid cabinet and base cabinet HIGH PRIORITY corrective action	**Quality Manager**	1	5	1	**5**
Isopropanol	Chronic inhalation during IR/HPLC rinsing	Chronic flammable vapour inhalation during IR spectrometry and HPLC	Irregular fume cupboard use for substances perceived as lower-risk; open containers during multi-step rinsing procedures	Chronic CNS depression; headache; dizziness; flammable vapour accumulation risk	4	3	2	**24**	Systematic fume cupboard use enforced for all volatile substance preparations; immediate re-capping	**Quality Manager + Laboratory Analyst**	2	2	2	**8**

		column rinsing continuous exposure							protocol added to SOP					
DMF (N,N-Dimethylformamide)	CMR Cat. 1B dermal absorption + inhalation	Chronic dermal absorption and inhalation of CMR Category 1B reproductive toxicant	Nitrile gloves used as default PPE insufficient barrier (breakthrough time < 1 work shift per GESTIS data); absence of butyl glove protocol for CMR substances	Reproductive toxicity (REACH Cat. 1B); hepatotoxicity; chronic dermal absorption risk most serious PPE gap in study	3	5	2	**30**	Replace nitrile with butyl gloves for all DMF handling (breakthrough >480 min); implement ambient air monitoring for DMF	**Quality Manager**	2	5	1	**10**
Karl Fischer Reagent	SO_2/methanol vapour inhalation no local extraction	SO_2 and methanol vapour inhalation during Karl Fischer titration NO fume cupboard at KF workstation (confirmed by observation + interviews)	Karl Fischer workstation has no dedicated local extraction; titration performed daily at open bench; engineering gap confirmed by all 3 interviewees	SO_2 inhalation: respiratory irritation, bronchospasm; methanol neurotoxicity from chronic daily exposure	5	4	1	**20**	Install dedicated local extraction unit at Karl Fischer workstation ENGINEERING PRIORITY 1 (most critical infrastructure gap)	**Quality Control Specialist + Quality Manager**	1	5	1	**5**
All Volatile Solvents	Vapour leaks from inadequate closures	Chronic diffuse VOC inhalation from inadequate stoppers/closur	Degraded or incompatible closures identified independently by ALL 3 interviewees; absent from all documentary sources	Highest criticality scenario (CI=36): chronic diffuse VOC inhalation across HPLC, UV-	4	3	3	**36**	Replace all inadequate closures immediately; add container closure verification to daily	**Quality Manager + Laboratory Analyst**	3	1	3	9

		es across all analytical operations HIGHEST CI IN STUDY	(GMP checklist, SDS, risk register)	Vis, Karl Fischer, IR operations; invisible to regulatory audit					SOP checklist; document in chemical risk register					
All Solvents / Waste	Mixing of hazardous waste in common containers	Halogenated, non-halogenated and acid waste mixed in same containers chemical incompatibility risk	Mixed HPLC mobile phases (acid + halogenated solvent) technically inseparable under current analytical setup; single-container waste collection	Chemical incompatibility in waste containers; toxic gas generation; fire risk; environmental contamination; regulatory non-conformity (Ch.7)	4	4	1	**16**	Implement separate labelled containers by chemical category; provide training on mixed mobile phase waste classification	**Laboratory Analyst + Quality Manager**	2	2	1	4