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Process integration of quality management systems, occupational health and safety, environment in pharmaceutical laboratories

Integração de processos dos sistemas gestão da qualidade, segurança e saúde ocupacional, meio ambiente em laboratórios farmacêuticos

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ABSTRACT

Introduction: Due to health regulations, the quality management system in pharmaceutical companies is compulsory and regularly evaluated by health bodies in relation to GMP supervision. However, health regulation does not extend to concerns about occupational health and safety and the environment. It is important to mature the management systems for these issues. **Objective:** To study the integration potential of occupational health and safety systems, environment and quality of pharmaceutical laboratories, considering the assumptions, regulatory requirements and particularities of the segment. **Method:** Exploratory and descriptive study carried out through documentary and field research. Matrixes of requirements of the thematic standards were built and mapped, and actions for integration were proposed. After that, they were submitted to the evaluation by specialists. **Results:** Comparing the RDC 301/2019 and 652/2022 with the ICH Q10, ISO 9001, 45001 and 14001, it was found that for 71% of the themes and normative requirements, there is synergy and total convergence between the requirements. For the other items, it is necessary to adapt processes and conducts. The propositions listed by the authors to address the gaps were positively validated in relation to achieving implementation feasibility in about 90%. In relation to the positive benefit, the evaluation was unanimous in 100%, and for the implementation of the resources listed, in 66% of the points there is a need for great institutional effort. **Conclusions:** The integration of a management system that incorporates the themes quality, health and safety and the environment is possible and beneficial for the pharmaceutical industry and supports the definition of strategies, prioritization of actions and allocation of resources.

KEYWORDS: Integrated Management System; Pharmaceutical Industry; Pharmaceutical Quality

RESUMO

Introdução: Por conta da regulamentação sanitária, o sistema de gestão da qualidade nas indústrias farmacêuticas é compulsório e regularmente avaliado pelos órgãos sanitários com relação à adequação às boas práticas de fabricação (BPF). Entretanto, a regulamentação sanitária não se estende às preocupações com a saúde e segurança ocupacional e com o meio ambiente. É importante amadurecer os sistemas de gestão destas temáticas. **Objetivo:** Estudar a potencialidade de integração dos sistemas de segurança e saúde ocupacional, meio ambiente e qualidade de laboratórios farmacêuticos levando em consideração as premissas, os requisitos regulatórios e as particularidades do segmento. **Método:** Estudo exploratório e descritivo realizado por meio de pesquisa documental e de campo. Foram construídas matrizes de correlação de requisitos das normas temáticas, mapeadas e propostas ações para integração e em sequência submetida a avaliação por especialistas. **Resultados:** Comparando as RDC n° 301/2019 e n° 652/2022 com o ICH Q10, ISO 9001, 45001 e 14001, constatou-se que,

para 71% dos temas e requisitos normativos, há sinergia e convergência total entre os requerimentos. Para os demais itens são necessárias adequações de processos e condutas. As proposições elencadas pelos autores para tratar as lacunas foram validadas positivamente com relação ao parâmetro viabilidade de implementação em cerca de 90%. Com relação ao benefício positivo, a avaliação foi unânime em 100% e, para a concretização dos tópicos elencados, para 66% dos pontos há necessidade de grande esforço institucional. **Conclusões:** A integração de um sistema de gestão que incorpore as temáticas qualidade, saúde e segurança e meio ambiente é possível e benéfica para a indústria farmacêutica e suportaria a definição de estratégias, priorizações de ações e alocação de recursos.

PALAVRAS-CHAVE: Sistema de Gestão Integrada; Indústria Farmacêutica; Qualidade Farmacêutica

INTRODUCTION

The importance of the pharmaceutical industry is intrinsically related to the impact it has on society, making it possible to treat diseases and increasing people's life expectancy. It is also one of the most important sectors of the economy in terms of job creation, income, and taxes collected[1].

However, understanding the complex relationship between scientific knowledge, technological innovation, and economic exploitation is the main challenge for science-based industries such as pharmaceuticals to remain competitive[2].

The pharmaceutical industry, like any public or private company, has a quality system as one of the main tools not only to achieve its objectives but also to foster continuous improvement processes[1].

In the pharmaceutical sector, quality is not only a tool for increasing competitiveness, it is also a compulsory factor for the sector to be able to operate its activities. For industries to be able to produce and distribute, they are regularly inspected to assess the adequacy of their quality system, which must be structured and correctly implemented, incorporating good manufacturing practices (GMP), in order to obtain the Good Manufacturing Practices Certificate (GMPC)[3]. No product subject to the health surveillance system, such as medicines, may be industrialized, offered for sale, or delivered for consumption before it has been registered with the competent health surveillance body.[4]

The overarching goal of the pharmaceutical quality system (PQS) is the consistent delivery of products with the appropriate quality attributes, which is achieved through the appropriate design, planning, implementation, maintenance and continuous improvement of the system itself[5]. The PQS must also ensure that product and process knowledge is managed throughout all phases of the life cycle and that it is used in the evaluation and improvement of processes in a way that is based on science and risk.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q10 lists the following stages that make up the life cycle of a medicine: pharmaceutical development, technology transfer, commercial manufacture, and product discontinuation[6]. Each of the phases of the drug's life cycle requires quality management, assurance, and control practices, processes, and techniques, which need to be provided for in the PQS. Clearly, then, in order to ensure regulatory compliance applicable to each phase of the drug's life cycle, this system must be robust and clearly defined and planned, executed, and monitored[7].

Paradoxically, despite being a segment that adds ultra-modern technologies and the great support provided by the GMPs for medicines set by health legislation, the medicines industry lives with various risks, such as those to the health of its workers and those associated with the environment[8].

There are many health problems for workers as a result of their activities in the pharmaceutical industry. The raw materials used in the production of medicines can rarely be administered as they are, and it is almost always necessary to subject them to a certain amount of manipulation in order to transform them into pharmaceutical forms[9]. In their activities, workers in the pharmaceutical industry can absorb drugs not because they want to or because they need to. There are also a number of physical, chemical, biological, ergonomic, and accident risks to be found in any manufacturing process.

In addition, in Brazil, every organization, regardless of its size and branch of activity, must compulsorily observe and comply with the set of requirements, provisions and technical procedures defined in the series of regulatory standards (NR) relating to occupational safety and medicine established by the Ministry of Labor and Employment and provided for in the set of labor laws (CLT). The NRs aim to provide people with health and safety when carrying out their professional activities[10]. There are currently 35 NR in force, and the applicability of each standard to the pharmaceutical industry depends on the nature of the work, activities and complexity of the production chain, inputs, facilities, products, and processes at each plant.

In this context, occupational health and safety (OHS) management (with a focus on eliminating danger and minimizing occupational risks) and environmental management (with a focus on eliminating/minimizing the environmental impacts of operations) are essential for providing safe and healthy workplaces, preventing work-related injuries and health problems, and taking effective preventive and protective measures. It is important for pharmaceutical companies to

focus not only on the safety of the medicines they supply but also on the safety of their employees and the environment in which they operate.

However, national pharmaceutical laboratories have adopted practices and standards that adhere to GMP, whose objective is focused on the quality of medicines and patient health, but they are still moving slowly towards the goal of a robust OHS management system that incorporates occupational and environmental risk management into its strategies and values[11].

Robust and strategic quality management is only complete if a virtuous cycle of planning, doing, checking, and acting - the PDCA cycle[12,13]. Similarly, the models presented for management systems propose the same PDCA cycle, such as the ABNT ISO 45.001 standard[14], which deals with the OHS management system, and the ABNT ISO 14.001 standard[15], which refers to the environmental management system.

Because of the similarities in the objectives, requirements, and processes of the various management systems, there is a tendency for organizations to integrate their systems by means of an integrated management system (IMS)[16].

Thus, in view of this scenario, understanding the importance of the quality management system for the pharmaceutical industry throughout the life cycle of the drug and envisioning the possibility of its interaction with other management systems, this study was carried out to verify the potential for integrating processes from the occupational health and safety and environmental management systems into the pharmaceutical quality management system, considering the regulatory premises and requirements and the particularities of the segment.

The study sought to answer the guiding questions of this work: is it possible to integrate the processes of the health, occupational safety (physical, chemical, biological, ergonomic, and accident risks), and environmental management systems with the pharmaceutical quality management processes? Does the integration of processes from the various management systems of pharmaceutical laboratories translate into gains for the institution?

METHOD

Initially, a literature review was carried out on the macro themes surrounding the study. A systematic search was carried out for articles and literature in scientific databases (such as: Web of Science, Scientific Electronic Library Online - SciELO, Scopus, PubMed, Google Scholar), journals, and institutional websites of interest such as: Pharmacists' Defence Association (PDA), Brazilian National Health Surveillance Agency (Anvisa), Food and Drug Administration (FDA), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), World Health Organization (WHO), Ministry of Labour, and Brazilian Association of Technical Standards (ABNT). For the search, keywords (initially defined as: pharmaceutical quality; quality management; environmental management; OHS management; integrated management systems), derivatives, and synonyms were defined, and the search was carried out using the keywords singularly and combined, in Portuguese and English. The search strategy included articles and literature from 2010 onwards. The study was then divided into three macro-stages.

In the first stage, a comparative analysis of the requirements was carried out. Initially, documentary research was carried out on Anvisa resolutions, ISO standards, and technical models mapped in the initial state-of-the-art survey, which were adopted according to the motivations in Chart 1.

After carrying out a documentary search of the regulations, the common requirements of the models were mapped, tabulated and compared in order to identify similarities, synergies, and divergences. The following topics and respective requirements were analyzed: management system planning; leadership; resources; operations/processes; procurement and outsourcing; infrastructure; personnel; documentation; product monitoring; relationships with interested parties; improvement processes; risk management and knowledge management; and management system performance evaluation.

In the second stage, based on the requirements mapped and assessed, an analysis was made of the processes that support meeting the theme/requirement of pharmaceutical GMP quality management systems with the other ISO standards. In this assessment, the potential for integration and the degree of effort and suitability for integrating processes and requirements were observed.

Finally, in the third stage to validate the integration proposal presented by the authors, the proposal was evaluated by professional specialists in the subject areas with expertise in the pharmaceutical sector. To define the profile of the research participants, the following criteria were defined: that they had a university degree and at least three years' experience in the pharmaceutical industry in the areas of occupational safety, environmental management, and quality management.

The questionnaire was designed in such a way as to obtain the participants' understanding and personal perceptions of the authors' proposal for integrating management processes and systems. Following the construction of the questionnaire, the field study project was submitted for evaluation by the Research Ethics Council (CEP) of the Oswaldo Cruz Foundation (Fiocruz), and was approved for application according to CEP Report No. 5.633.011. The project included the use of a structured electronic questionnaire to facilitate access and participation on the Google Forms platform. A total of 27 participants were invited, three employees from each thematic area, totaling nine employees per participating company. The data collection period was between August and December 2022 and it took two months to receive 27 fully completed questionnaires. After collection, the data was tabulated and evaluated.

RESULTS AND DISCUSSION

Comparative analysis of requirements

By correlating the requirements of the pharmaceutical quality and GMP management system applied to the life cycle of the drug and defined as compulsory by Anvisa's Resolutions of the Collegiate Board (RDC), with the model proposed by ICH Q10 and with the requirements of the ABNT ISO 9001:2015, ISO 45001:2019, ISO 14001:2015 standards, the situation of convergence/divergence of requirements and processes shown in Chart 2 was identified.

Of the 13 themes evaluated, five are totally convergent in all the standards (management system planning, leadership, resources, documentation, and management system evaluation) and two have requirements that are convergent and requirements linked to the theme that are not identified, i.e., are absent from the standards (personnel and product monitoring). In this case, it is understood that there is no degree of impact or difficulty, since the absent requirement is not the object of implementation. In this sense, the themes were added together and considered to be totally convergent, giving a total of seven themes (management

Chart 1. Motivations for legislation/standards adopted for comparison and analysis.

Model/Standard selected	Motivation
RDC Anvisa No. 17/201017	General guidelines for good drug manufacturing practices approved in 2010 - Resolution that had as a reference the WHO GMP guidelines from 2003.
RDC Anvisa No. 301/201919	General guidelines for good drug manufacturing practices approved in 2019 in Brazil - Resolution that had as a reference the GMP guidelines of the PIC/S of 2019.
RDC Anvisa No. 658/202220	General guidelines for good drug manufacturing practices approved in 2022, which basically maintained the previous text with small text and spelling adjustments to facilitate understanding.
ICH Q10	Pharmaceutical quality management system model described by ICH and adopted by regulatory authorities in the USA, the European Union, and Japan.
ABNT NBR ISO 9001:2015	Quality management system model widely adopted by different segments and internationally recognized. The ISO 9000 series provides a model for process management, which guides organizations in the specifications, documentation and maintenance of a quality management system in order to make it effective[21].
ABNT NBR ISO 14001:2015	Environmental management system model widely adopted by different segments and internationally recognized.
ABNT NBR ISO 45001:2018	Health and safety system model widely adopted by different segments and internationally recognized.

Source: Prepared by the authors, 2023.
RDC: Resolution of the Collegiate Board; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ABNT: Brazilian Association of Technical Standards; GMP: Good Manufacturing Practices; WHO: World Health Organization; PIC/S: Pharmaceutical Inspection Convention.

Chart 2. Summary of the tabulation of the integration potential and level of efforts of the requirements.

Theme	ICH Q10 - Pharmaceutical Quality System	NBR ABNT ISO 9001 - Quality Management System	ISO 45001 - Health and Safety Management System	NBR ABNT ISO 14001 - Environmental Management System
Management system planning	C	C	C	C
Leadership	C	C	C	C
Resources	C	C	C	C
Operations/processes	A	NS	NS	NS
Acquisition and outsourcing of activities	C	C	NS	NS
Infrastructure (facilities and equipment)	A	NS	NS	NS
Staff	A	C	C	C
Documentation	C	C	C	C
Product monitoring	C	C	A	A
Stakeholder relationships	C	C	NS	NS
Improvement processes	C	C	NS	NS
Risk and knowledge management	C	NS	NS	NS
Management system performance assessment	C	C	C	C

Source: Prepared by the authors, 2023.
A (absent), in blue, indicates that the requirement is not included in the text; C (convergent), in green, indicates that the requirement is contained in the text and the provisions are convergent with Anvisa's good manufacturing practice regulations; NS (not similar), in yellow, indicates that the theme text has the theme's approach, but the focus is not similar; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ABNT: Brazilian Association of Technical Standards.

system planning, leadership, resources, documentation, system evaluation, personnel management, and product monitoring).

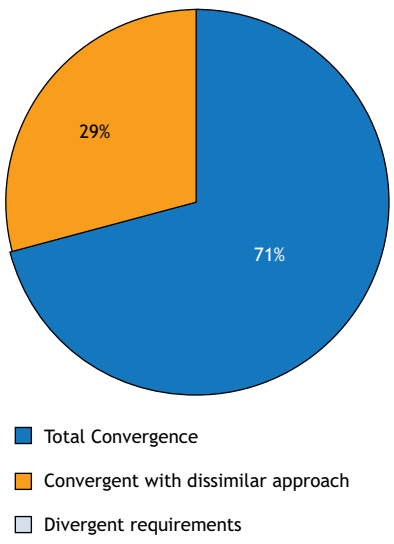
Four themes have converging requirements and requirements with non-similar approaches (acquisition and outsourcing of activities, relationships with stakeholders, improvement processes and risk management, and knowledge management). The effort is focused on implementing and improving processes to incorporate the new approaches. Two themes (operations and processes and infrastructure) have requirements whose approach, although convergent, is not similar and some requirements have not been identified in the texts of the standards. In the latter case, it is understood that there is no degree of impact or difficulty since the missing requirement is not the object of implementation. Regarding the condition of divergence between the requirements and the topics, the condition was not met.

Regarding the distribution of the 52 requirements in terms of the degree of convergence with the four standards studied, the mapped scenario is shown in Figure 1.

The scenario shows that, for the most part, there is synergy and convergence between the requirements and, in principle, this structure would facilitate and ensure coherence and compatibility for the association of management systems. Regarding the requirements where convergence has been identified but with a different approach, a series of process and conduct adjustments are necessary, as described below.

Analysis of potential and degree of effort to integrate processes

Based on the assessment of the potential for integrating processes and requirements and the respective degrees of effort and suitability, the following scenario emerges:



Source: Prepared by the authors, 2023.

Figure 1. Requirements distribution graph by degree of convergence.

Planning management systems

Regarding the potential for integrating processes that support the planning of management systems, it was observed that this is feasible and that it would not require much additional effort beyond the aspects already legally pointed out and required by health regulations, which provide for the same model based on PDCA and continuous improvement. The observation of efforts identified the following needs:

- revision of the quality policy which, when integrated, must incorporate the global principles and objectives of occupational health and safety (OHS) and environmental management, commitment to continuous improvement, and compliance with current legislation;
- the organization must map and document the environmental aspects and impacts associated with its processes and operations and the respective control systems;
- the organization must map and document the occupational hazards and risks associated with its processes and operations and the respective control systems.

Leadership

In the ISO series of standards, in addition to the requirements already provided for in health legislation, the expectation of the role of top management is established in detail and must be evidenced in other aspects, such as: demonstrating commitment to the management system, knowledge of the risk approach, establishing, and making compatible policy and objectives with the organization's strategy; integrating the requirements of the management system into business processes; making resources available; effective communication; developing leadership and organizational culture; promoting continuous improvement, demonstrating consultation and participation of workers, establishing specific technical committees and promoting critical analysis of systems.

The observation of efforts identified the following needs:

- reorientation of responsibilities, mentality, engagement in driving, monitoring, and leadership by senior management in the integration of management systems;
- prioritizing and making resources available for incorporating requirements;
- reorientation and assimilation of responsibility for management systems at all hierarchical levels;
- consultation and participation of workers at all levels and in all phases of IMS implementation (development, planning, implementation, performance evaluation, and improvement actions).

Resources

Regarding the requirements related to resources, it was found that the subject is covered in all the standards, models, and legislation studied. However, it was noted that the resources

scored and required in the GMP-related legislation were more detailed than in the others, as they include resources directly related to production processes and the pharmaceutical environment, such as facilities, equipment, and instruments. No additional efforts were made to integrate the integrated management system with the pharmaceutical quality management system in relation to this requirement.

Operations

Although the requirements of the Operations theme are present in all the standards, models, and legislation studied, this theme included a description of the particularities of each management system model studied, as well as the GMP legislation. The proposals presented for integrating this theme include:

- implementing operational procedures and controls in business processes (value chain) with a focus on environmental management and OHS management;
- implementation of processes and procedures for managing environmental aspects and impacts, including controls aimed at: elimination/mitigation, substitution, engineering controls, work organization, and administrative controls;
- implementation of occupational risk management processes and procedures, including controls aimed at eliminating hazards/risks, substitution, engineering controls, work organization, and administrative controls;
- implementation of a process to control planned temporary and permanent changes that impact environmental performance and OHS requirements;
- implementation of a process to manage changes in legal requirements (regulatory framework) and the development of knowledge and technology in terms of environmental performance and OHS requirements;
- implementation of processes and procedures to prepare for responses to possible environmental and OHS emergencies.

Procurement (inputs, products, and services) and outsourcing

The GMP legislation contains an external and detailed list of requirements for raw materials and product inputs and, consequently, for the suppliers of these items. Requirements range from the application of the risk management approach to defining inputs and suppliers that are critical to product quality, drawing up specifications for the purchase and quality control of materials, qualification, and audits of suppliers, as well as requirements for the various material processes in the organization, such as: receiving, storage, sampling, quality control tests, fractionations, deliveries, use, records of operations, and specifications with quality parameters. The ISO 9001 standard also addresses the issue by relating controls to processes and products and services, in this case those provided externally.

In ISO 45001 and 14001, the requirements for this topic are related to the need to ensure that services, activities, and operations carried out through contractors comply with the contractor's management system and other relevant legal requirements. The proposals presented for integrating this theme include:

- inclusion of OHS and environmental management criteria in the procurement of materials/inputs and in the selection of suppliers;
- establishment of processes that address operational controls and monitoring of suppliers and partners in order to ensure that environmental and safety requirements are met in activities and operations.

Infrastructure

Although the requirements of the Infrastructure theme are present in all the standards, models, and legislation studied (with the exception of ICH Q10), it was found that the approach to the theme is different, as is the extent and level of detail of the requirements. In ABNT ISO 9001 and 14001 standards, the item is dealt with in a generic way, being one of the resources cited as necessary to support and operate processes. In ISO 450001, infrastructure is mentioned as an item to be taken into consideration when planning the system, in order to identify dangers and assess risks and opportunities arising from the infrastructure.

In the health legislation related to GMP, it was observed that the requirements related to facilities and equipment are extensively punctuated and detailed, ranging from the conceptual discussion of layout projects and construction materials in order to avoid product contamination, as well as specification and acquisition, construction, qualification cycles, maintenance, and systematic checks on the correct functioning of equipment and the suitability of facilities. The proposals presented for integrating this theme include:

- when planning the layout of facilities and purchasing equipment/instruments, full compliance with the various NRs related to OHS must be observed: NR 8 - Buildings, NR 10 - Safety in electrical installations, NR 12 - Safety at work in machinery and equipment, NR 13 - Boilers, pressure vessels, metal storage tanks, NR 14 - Furnaces, NR 20 - Health and safety at work with flammable and combustible materials, NR 23 - Fire protection, NR 24 - Sanitary and comfort conditions in the workplace, NR 25 - Industrial waste, NR 26 - Safety signs, NR 33 - Health and safety at work in confined spaces, NR 35 - Working at heights. Each NR covers an extensive list of requirements that may or may not be applicable depending on the layout/type of equipment;
- when planning the layout of facilities and purchasing equipment/instruments, full compliance with the various standards and legislation relating to environmental management must be observed;

- implementation of procedures in the user requirements specification (URS) drafting and procurement processes that take into account compliance with OHS and environmental management requirements, as well as operational control procedures to ensure that requirements are met by contractors and outsourcers in routine activities and operations;
- the inclusion of occupational safety and environmental management criteria in the definition of the preventive maintenance plan for installations and equipment/instruments, so that the criticality and risk related to these issues are taken into account in the periodicities;
- inclusion of occupational safety and environmental management criteria in the definition of the process validation plan and qualification of critical and high-risk equipment/instruments related to these themes.

Staff

Regarding the requirements related to personnel, it was found that the subject is covered in all the standards, models, and legislation studied (except for the ICH Q10 model), although the legislation related to GMP is more detailed than the others. In addition to the points about the appropriate number of staff and the skills required (common to all standards), GMP legislation points out aspects related to the attribution and responsibilities of key staff (including the role of the technical manager) and determines requirements related to conduct, hygiene, and staff training, in order to avoid impacts on products resulting from human factors.

Among the proposals put forward to integrate this issue, the following stand out:

- definition and description of functions with duties and responsibilities;
- establishing initial training and continuous improvement practices in relation to OHS and environmental management;
- establishment of internal and external communication practices on the ISO 9001, 45001, and 14001 standards that convey and disseminate the concept and approach, the benefits and relevance for employees, interested parties and the organization, as well as the dissemination and internalization of the contribution of each function/employee in the implementation/maintenance of the management systems.

Documentation

In this study, no major additional efforts were made to integrate the integrated management system from the pharmaceutical quality management system regarding the documentation management process due to the high level of requirements and demands related to documentation in the pharmaceutical health legislation. However, specific documents and procedures defined in the ISO standards should be drawn up or revised, such as the integrated management system policy and manual.

Product monitoring

Regarding the issue of product monitoring, requirements were identified in all the quality-related standards and legislation studied, including GMP, ICH Q10, and ISO 9001, although the GMP standards were more detailed and rigorous than the others. The ISO 45001 and 14001 standards did not map any requirements directly related to product monitoring. No additional efforts were made to integrate the integrated management system.

Relationships with stakeholders

Although the requirements of the Relationship with interested parties theme are present in all the standards, models, and legislation studied, in this theme we observed a description of the particularities of each management system model studied, as well as the GMP legislation.

The GMP legislation contains an external and detailed list of requirements focused on the patient and health authorities. Regarding standards, the ISO 9001 standard also addresses the issue by relating the need for communication from the customer's point of view, which goes from gathering expectations and needs and then establishing processes for evaluating satisfaction and product performance. In addition, the ISO 9001 standard, as well as ISO 45001 and ISO 14001, broadens the concept of interested parties beyond the patient/customer and the need to understand these expectations, such as: suppliers and partners, employees, partners/shareholders, the community, and competitors. The proposals presented for integrating this theme include:

- implementing procedures and processes for mapping, monitoring expectations, and communicating with stakeholders;
- implementing practices to improve inter-institutional relationships.

Risk management and knowledge management

Regarding the requirements related to risk management, the approach and concept were identified in all the standards, models, and legislation studied. In all of them, the concept of a risk mentality is highlighted as essential and intrinsic to the planning of the management systems system, permeating the processes in a systemic way.

The difference lies in the applicability and specificity of the standard and legislation: in GMP, ICH Q1O, and ISO 9001, the risk is assessed with a focus on product quality and patient safety. In ISO 45001, the approach is applied to risks relating to the health and safety of employees, and in ISO 14001 the risk is addressed in relation to the possible environmental impacts of the organization's operations.

In essence, GMP requirements are primarily aimed at reducing the risks inherent in any pharmaceutical production and cannot be detected solely by carrying out tests on finished products[18]. The main health risks associated with pharmaceutical

production that GMP aims to reduce are: cross-contamination, product contamination and product exchange or mixing. Regarding ISO standards, since the publication of ISO 3100 - Risk Management - Principles and Guidelines in 2009, ISO standards have been revised to incorporate the concepts and thinking based on risk and knowledge management. The ISO 9001 version 2015, ISO 14001 version 2015, and ISO 45001 version 2018 standards include the concept of risk mentality comprehensively and explicitly in several of their requirements. The proposals presented for integrating this theme include:

- establishment, implementation, and maintenance of an occupational risk management program;
- establishment, implementation, and maintenance of an environmental aspects/impacts management program.

Performance evaluation of the management system

Regarding the requirements related to evaluating the performance of the management system, it was found that the subject is covered in all the standards, models, and legislation studied.

In the current version of the GMP RDC, in addition to internal quality audits in the production and support processes of the management system, the need to implement processes that support the performance measurement of the management system is defined, such as: implementation and management of performance indicators, as well as processes for reporting, analysis, management review, and decision-making by senior management on the performance and effectiveness of the management system, with the so-called critical analyses.

Among the proposals put forward to integrate this issue, the following stand out:

- establish, implement, and maintain a process for carrying out internal audits based on the requirements of ISO 45001 and ISO 14001;
- establish, implement, and maintain a process for managing the performance and effectiveness of the environmental and OHS management system that includes critical analysis by senior management.

Improvement processes

Regarding the requirements related to the topic of Improvement Processes, it was found that the topic is covered in all the standards, models, and legislation studied. In all of them, the improvement process is conducted through the process of identifying and investigating non-conformities and their respective root causes, implementing actions aimed at preventing the non-conformity from recurring, as well as assessing the effectiveness of the corrective/preventive actions taken. The concept of non-conformity, however, changes according to the specificity of each standard.

In ISO 45001, the concept of non-conformity is geared towards maintaining OHS conditions. In this concept, the approach is focused on non-conformities, incidents, and accidents at work, reflecting the standard's objective of preventing injuries and illnesses and providing safe and healthy workplaces for workers.

In the ISO 14001 standard, the concept of non-conformity is geared towards maintaining adequate environmental performance. In this concept, the approach is focused on non-conformities and environmental impacts. For the ISO standards (9001, 45001, and 14001), in addition to the requirements for managing non-conformities and the Corrective Action and Preventive Action (CAPA) system, the concept of improvement must be broadened and the organization must determine and select opportunities for improvement and implement any actions necessary not only to adequately maintain the defined standards but also to proactively address future needs and expectations. The proposals presented for integrating this theme include:

- establish, implement, and maintain a process for managing incidents and accidents at work, including the CAPA system;
- establish, implement, and maintain a process for managing environmental non-conformities, including the CAPA system;
- establish, implement, and maintain a process for managing improvement opportunities;
- establish, implement, and maintain a process to manage the performance and effectiveness of the OSH management system;
- establish, implement, and maintain a process to manage the performance and effectiveness of the environmental management system.

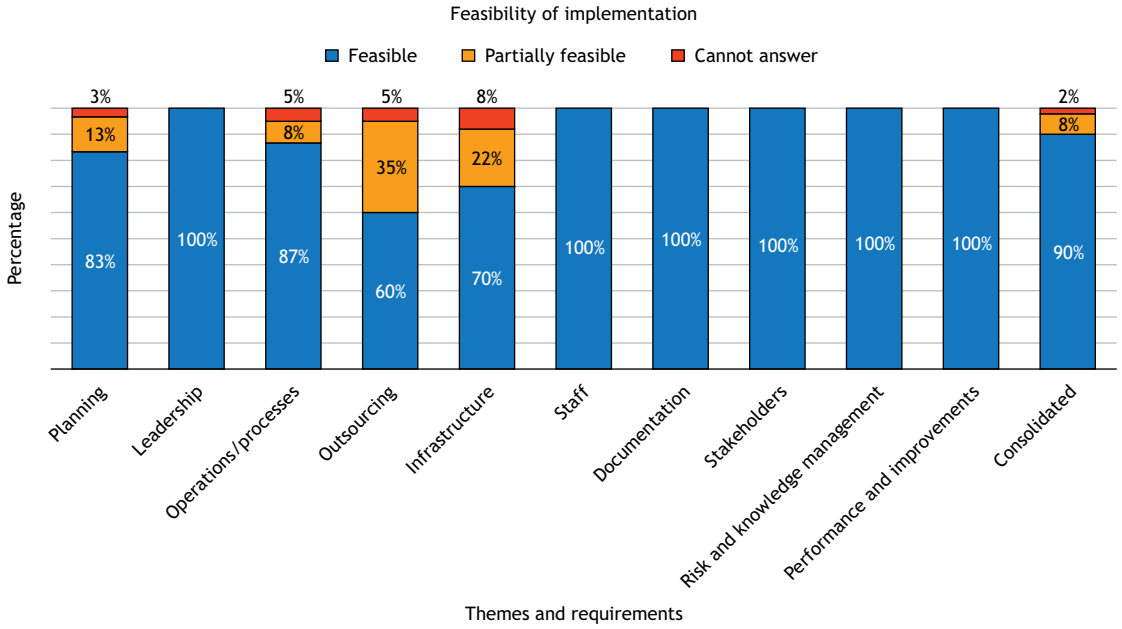
Validation and experts' perception of the integration proposal

Summarizing the result of the objective of this stage of the study, the purpose of which was to obtain the assessment of a group of specialists in the themes of OHS, the environment and quality regarding the proposals in relation to the parameters of feasibility, benefit, and institutional effort, we have the following scenario.

Regarding to the feasibility of implementing the proposals, the perception of all the participants regarding the general set of themes is positive for the integration of management system processes (Figure 2).

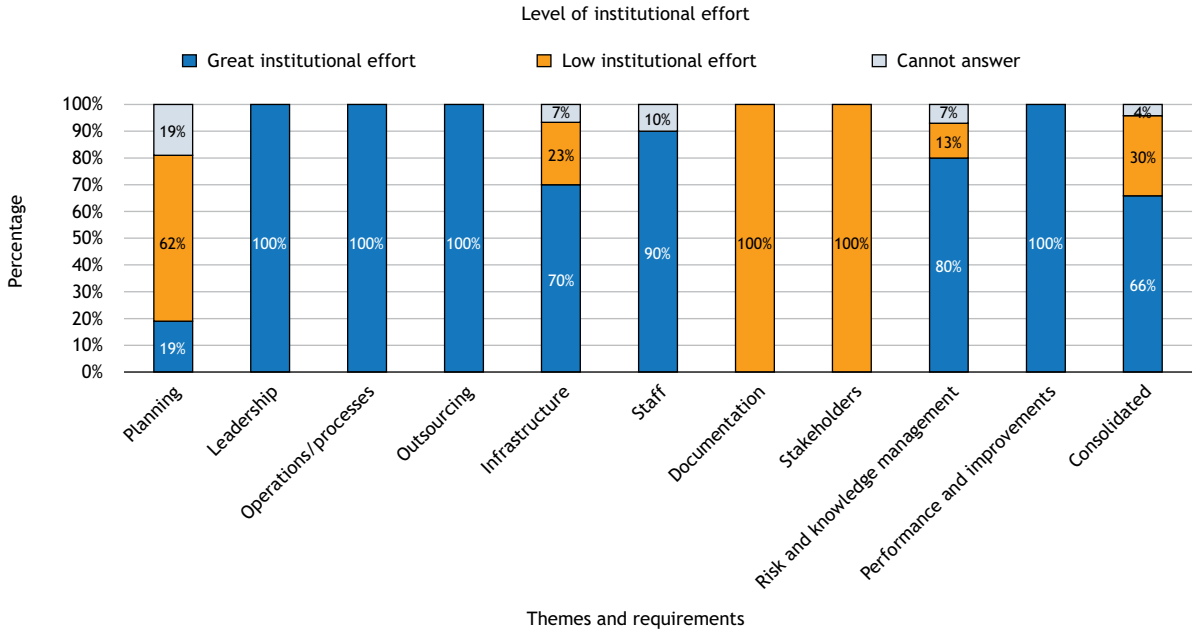
Regarding the benefit assessment, the perception of all the experts was unanimous on all the topics, and the result of implementing the proposed integrations was considered positive in 100% of the topics.

Regarding institutional effort, the perception is that a great deal of institutional effort is needed to achieve the topics listed for most of the themes (Figure 3).



Source: Prepared by the authors, 2023.

Figure 2. Assessment of the feasibility of implementing integration proposals.



Source: Prepared by the authors, 2023.

Figure 3. Level of institutional effort of integration proposals.

CONCLUSIONS

The exploratory literature review showed the evolution of the concepts, approaches, requirements, and obligations related to each theme and allowed us to raise a relevant question about the potential for integrating quality, occupational health and safety, and environmental management systems in pharmaceutical laboratories. The comparative studies of the requirements of regulations RDC No. 301/2019, ICH Q10, ISO 45001, ISO 9001, and ISO 14001 showed that there is synergy and convergence between the requirements, and in principle this structure would facilitate and ensure coherence and compatibility for the association of management systems.

Sequentially, the processes that support the requirements of the ISO standards were examined against the pharmaceutical health

legislation and, as a result, a set of proposals was drawn up to address the existing gaps and shortcomings in order to enable the integration of management systems.

The proposals for implementing/improving processes based on this study were reported to a group of technical experts in the areas of pharmaceutical quality, OHS, and the environment, who gave their opinion on the feasibility, the benefit to be achieved, and the level of institutional effort for each topic.

The survey of expert participants confirmed the propositions developed and discussed in the study and answered the study's guiding questions. Is it possible to integrate processes from health, occupational safety, and environmental management systems into pharmaceutical quality management processes?

Does the integration of processes from the various pharmaceutical laboratory management systems translate into gains for the institution?

By integrating a set of interrelated processes, it will be possible to share a set of resources: human, financial, material, as well as infrastructure, systems, and information, in order to achieve a set of objectives related to the satisfaction of various stakeholders. In this sense, processes, methods, and techniques can be defined uniformly, unified and integrated in order to meet the needs and expectations of customers and employees, reduce costs, reduce rework, reduce risks of various kinds, speed up processes, increase management capacity, and boost productivity.

It is concluded that the integration of a management system that incorporates the themes of quality, health and safety, and the environment is possible and beneficial for the pharmaceutical industry and would support the organization in defining strategies, making decisions and prioritizing actions, and allocating resources, and will fill the gap in providing more efficient mechanisms for the processes of health and safety and environmental management systems in the pharmaceutical industry.

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Authors' Contribution

Horato CM, Costa JCS - Conception, planning (study design), acquisition, data analysis, and writing of the work. All the authors approved the final version of the work.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.