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Risk management following international standards in the routine of an umbilical cord blood bank

Gerenciamento de riscos seguindo padrões internacionais na rotina de um banco de sangue de cordão umbilical

Gestión de riesgos siguiendo estándares internacionales en la rutina de un banco de sangre de cordón umbilical

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Abstract
This work demonstrates the main elements of the risk management system at a Brazilian umbilical cord blood bank, taking into account the criticality and individuality of the procedures as well as regulatory and certifying agency guidelines. This study involved the implementation of a Risk Management Committee which was responsible for process flow mapping; identifying, analyzing, classifying, treating, and monitoring risks using brainstorming, flowcharts, Pareto distribution, Ishikawa diagrams, and FMEA. Almost 900 risks were divided into 16 sectors, with 24% of total risks in the Blood Processing sector, demonstrating a strong relationship between critical activities and exposure to risks. Occurrence and severity were defined, followed by risk treatment and monitoring. The risk management system provided a more reliable infrastructure to customers and employees, upgraded the capabilities of the company, successful ISO 9001: 2015 certification, and renew American Association of Blood Bank accreditation. This paper presents a specific look at the implementation of a risk management system in a private umbilical cord blood bank. Typically, this sort of information is kept in internal company documents and is not widely disclosed in the literature. In this sense, this study presents a useful perspective for practitioners and academics.
Keywords: Blood bank; Quality management; Risk analysis; Healthcare failure mode and effect analysis; Stem cells.

Resumo
Este trabalho demonstra os principais elementos do sistema de gerenciamento de risco em um banco de sangue de cordão umbilical brasileiro, levando em consideração a criticidade e a individualidade dos procedimentos, bem como as diretrizes dos órgãos reguladores e certificadores. Este estudo envolveu a implantação de um Comitê de Gestão de

Riscos responsável pelo mapeamento dos fluxos dos processos; identificar, analisar, classificar, tratar e monitorar riscos usando *brainstorming*, fluxogramas, distribuição de Pareto, diagramas de Ishikawa e FMEA. Quase 900 riscos foram divididos em 16 setores, com 24% do total de riscos no setor de Processamento de Sangue, demonstrando forte relação entre atividades críticas e exposição aos riscos. A ocorrência e a gravidade foram definidas, seguidas do tratamento e monitoramento do risco. O sistema de gerenciamento de risco forneceu infraestrutura mais confiável para clientes e funcionários, melhorou as capacidades da empresa, contribuiu para a certificação ISO 9001:2015 bem-sucedida e renovação da certificação junto à Associação Americana de Bancos de Sangue. Este trabalho apresenta olhar específico sobre a implementação do sistema de gestão de risco em banco privado de sangue de cordão umbilical. Normalmente, esse tipo de informação é mantido em documentos internos da empresa e não é amplamente divulgado na literatura. Nesse sentido, este estudo apresenta perspectiva útil para profissionais e acadêmicos.
Palavras-chave: Banco de sangue; Gestão da qualidade; Análise de risco; Análise do modo e do efeito de falhas na assistência à saúde; Células-tronco.

Resumen

Este trabajo demuestra los principales elementos del sistema de gestión de riesgos en un banco de sangre de cordón umbilical brasileño, teniendo en cuenta la criticidad y la individualidad de los procedimientos, así como las directrices de las agencias reguladoras y certificadoras. Este estudio involucró la implementación de un Comité de Gestión de Riesgos que se encargó del mapeo del flujo de procesos; identificar, analizar, clasificar, tratar y monitorear riesgos usando lluvia de ideas, diagramas de flujo, distribución de Pareto, diagramas de Ishikawa y FMEA. Casi 900 riesgos se dividieron en 16 sectores, con un 24 % del total de riesgos en el sector de procesamiento de sangre, lo que demuestra una fuerte relación entre las actividades críticas y la exposición a los riesgos. Se definió la ocurrencia y severidad, seguido del tratamiento y seguimiento del riesgo. El sistema de gestión de riesgos proporcionó una infraestructura más confiable para clientes y empleados, mejoró las capacidades de la empresa, logró la certificación ISO 9001: 2015 y renovó la acreditación de la Asociación Estadounidense de Bancos de Sangre. Este trabajo presenta una mirada específica a la implementación de un sistema de gestión de riesgos en un banco privado de sangre de cordón umbilical. Por lo general, este tipo de información se guarda en documentos internos de la empresa y no se divulga ampliamente en la literatura. En este sentido, este estudio presenta una perspectiva útil para profesionales y académicos.
Palabras clave: Banco de sangre; Gestión de la calidad; Análisis de riesgo; Análisis de modo y efecto de fallas en la atención de la salud; Células madre.

1. Introduction

Stem cells are promising alternatives in disease therapy, particularly in cerebral palsy and autoimmune diseases (de Moraes, et al., 2022). The number of clinical applications of the umbilical cord and placental blood, which contain stem cells, has shown an important increase since its first use in 1988 (Gluckman, et al., 1989). Following this movement, umbilical cord blood banks (UCBB) emerged and improved their procedures over the years. These activities have been carried out in Brazil since the late 1990s by specialized companies, both public and private. Since then, this activity has developed and gained notoriety through scientific research carried out in various institutions (Pandey, et al., 2016).

The services provided by UCBB have immeasurable value since it involves the processing of a unique material rich in young stem cells, which can save or significantly improve the quality of life of patients. From the collection to the dispensing of the material to the patient there are many steps subject to risks derived from human errors in the execution of procedures, equipment failures, material deficiencies, and environmental issues, among others. Maintaining the proper conditions of temperature and pressure, in addition to slow and gradual freezing, these cells can remain stored for more than 50 years (Broxmeyer, et al., 2011).

For these reasons, umbilical cord blood processing must be defined by good practices, well-executed, and constantly controlled to guarantee high-quality standards (Brazil, 2018; Food and Drug Administration, 2019). UCBB are regulated by Food and Drug Administration (FDA) in the United States of America since the 1990s and in Brazil since 2003 by the Brazilian Health Regulatory Agency (ANVISA) (Brazil, 2003; Risso, et al., 2018).

Risk Management System (RMS), as a part of the Quality Management System, increases the reliability of this service by corrective and preventive actions throughout all stages of the production cycle (ISO, 2018; Lopez, et al., 2010). According to the International Conference on Harmonization (ICH), the risk is defined as a combination of probability and impact of the

damage (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 2005). For effective risk management, different systems and quality management tools can be applied in processes aiming at the minimization of risks, standing out, Brainstorming, Flowchart, Pareto Distribution, Ishikawa Diagram, and Failure Mode and Effects Analysis (FMEA) (Tague, 2005; Bambi, et al. 2009).

Although RMS is not required by ANVISA (Brazil, 2018), some companies implement it to increase the quality of services. The International Organization for Standardization (ISO) and the American Association of Blood Bank (AABB) establish the RMS as one of the requirements for the certification and accreditation of companies.

The ISO 9001:2015 certification is related to the Quality Management System and addresses topics such as leadership, risk and opportunity mentality, customer satisfaction, product quality, process control, and improvement, among other aspects (ABNT, 2015). This is one of the most well-known standards, used by thousands of organizations, and requires a risk management approach. This requirement helps companies to identify and assess the main risks in their process, creating a preventive action mentality, minimizing negative effects, and proposing actions to improve processes, to avoid possible deviations (ISO, 2015).

Accreditation by AABB presents detailed requirements at managerial and operational levels of blood banks, according to the view of specialists in this area. Its main function is related to the improvement of efficiency, quality, and safety of the whole area of hemotherapy services. All AABB audits must be carried out by specialized and trained professionals and be based on the "8th edition of Standards for Cellular Therapy Services" guide (American Association of Blood Banks, 2017). The institutions that are accredited by the AABB are leaders in their field of activity and only 3 out of 33 Brazilian UCBB have this certification ("AABB Accredited Cord Blood (CB) Facilities," n.d.).

This work shows the interventions carried out in the company Cryopraxis®, the biggest private umbilical cord blood bank in Brazil. The aim was the implementation of an RMS in the company Cryopraxis®. The Risk Management Committee (RMC) was responsible for process flow mapping; identifying, analyzing, classifying, treating, and monitoring risks.

2. Methodology

Description of company - Cryopraxis®

Cryopraxis Cryobiology, also called Cryopraxis®, is a biotechnology company created in 2001, which is dedicated to the collection, transportation, processing, cryopreservation, storage, and dispensation of human cells and tissues for therapeutic use. It was the pioneer company in Brazil for the collection and storage of umbilical cord and placental stem cells, and is already the largest company in the field in Latin America, investing in research and development.

Recently, Cryopraxis® expanded the storage capacity to more than 100,000 samples in a 1400 ft^2 structure containing cryogenic systems following international quality standards. With the increase in storage scale, the need for a review of risk management emerged.

Creation of the Risk Management Committee (RMC)

The RMC was composed of a multidisciplinary team, which had the representation of at least one member of each sector of the company, including the Medical Director, Customer Service, Collection, Laboratory (including processing, cryopreservation, storage, and dispensation for use), After Birth Service, Quality Assurance, Purchasing, Marketing, Information Technology, Research and Development, Warehousing, Finance, and Human Resources. The attributions of the RMC included scheduling meetings and training individually with each sector, presenting risk management methodologies, and producing study materials for employees.

Processes Flow Mapping

Process mapping was constructed with the Bizagi Modeler® System (version 3.1.0.0.11), including steps from the service commercialization stage to dispensation for use of the biological material. Process mapping was validated by RMC by checking the steps where they are routinely performed (on-site) (Lopez, et al., 2010). Such checks were carried out on pre-scheduled visits with the heads of each sector, where the information was checked through photo and video records.

Risk Identification, Analysis, and Classification

Firstly, brainstorming with RMC members was used for risk identification, following the processes flow mapping, the experience of co-workers in each sector, and quality deviations data in computerized records. The number of risks by sector was used to create a Pareto chart (Lopez, et al., 2010; Tague, 2005), which was used to establish the frequency of occurrences, from the highest to the lowest, allowing the prioritization of actions.

Another approach used to identify, analyze and classify risks was the FMEA (Bambi, et al., 2009; Tague, 2005), which incorporates a system to classify the impact of failure modes and prioritize corrective measures. A risk impact and probability scale was developed for evaluation before (pure risk) and after treatment actions (residual risk).

The root causes of risks were assessed according to the following categories of the Ishikawa Diagram: Methods, Machines (equipment), People (manpower), Materials, Measurement, and Environment.

Risk Treatment and Monitoring

New brainstorming cycles were held to determine the risk response strategies (mitigate, share, avoid or accept) according to the individualities of each situation. In this way, the RMC established responsibilities, deadlines, and risk priority, as well as the necessary resources for each stage.

Risk treatment included the introduction or modification of technologies; preparation or review of documents to minimize risks; training and even modifications to existing processes. All control measures, already existing in the company or that applied during FMEA, were documented in the Risk Management spreadsheets of each sector. In some cases, more than one control measure was necessary to control a hazard, or more than one hazard was controlled by the same control measure. To carry out the monitoring, the Plan-do-check-act (PDCA) Cycle approach was applied (Deming, 2000; Tague, 2005) by checking and acting during the monitoring of the processes to minimize or extinguish residual risks.

3. Results and Discussion

The company had a Risk Management System that did not contain all the elements necessary for the AABB accreditation and ISO 9001 certification since it implicitly acted on potential risks and non-conformities through preventive actions. Most of the actions determined by the certification bodies were already carried out by the company, but they were not formally described in a Risk Management System, standard operating procedures (SOP), and other internal documents. Seeking to follow international standards, the company invested efforts to create a risk management system capable of identifying, minimizing, and monitoring new or pre-existing risks and guaranteeing the continuous improvement of processes.

The hierarchical organization of the RMC initially worked with the quality assurance sector and the company's technical board, representing the company's directors. RMC meetings included 21 members from different sectors of the company and it was necessary to clarify RMS steps, from the processes flow mapping to the document review and data presentation in audits by the certification and accreditation agencies. Some members were from the same sector, as they had a fundamental role due to the degree of competence and experience to carry out their activities, and their participation in the process was extremely important.

One of the first assignments of the RMC members was the participation in external training on the interpretation of ISO 9001:2015 (ISO, 2015) and ISO 31000:2018 (ISO, 2018) standards. During 3 days, they were trained in basic concepts and structure of the ABNT NBR ISO 9001:2015 standard, quality management system, evaluation, and implementation of minimum requirements, exercises, and case study. The training program of the ABNT NBR ISO 31000:2018 standard was directed to the benefits and applications of risk management; basic concepts, definitions, and introduction to ISO 31000:2018, including its scope, principles, the structure of the standard, and how the risk management process is organized (ABNT, 2018).

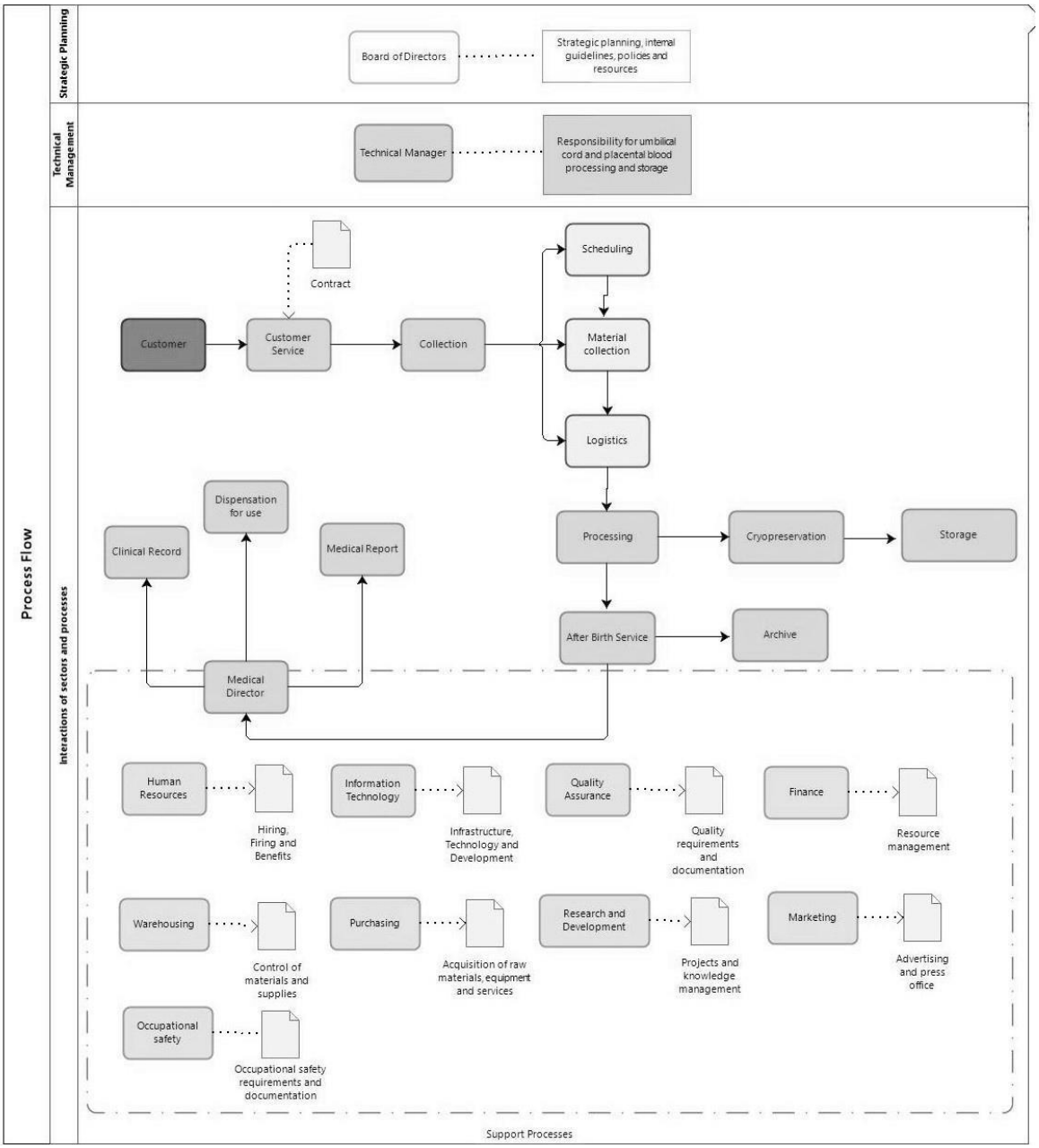
Subsequently, the members of the RMC acted as multipliers of this training to the other employees, using the ISO 9001:2015 and ISO 31000:2018 standards as a basis, in addition to tools such as brainstorming; Ishikawa diagram; FMEA; Failure mode effects and criticality analysis (FMECA); 5W2H, 5 Whys. Periodic meetings were held with the teams to spread the risk management mindset and tools and, since then, the same system has been used for continuous training and as a means of reminding the team of the importance of Quality Management.

Technical standards documents (Brazil, 2018; ISO, 2018; ISO, 2015) and training materials (slideshows with risk management process definitions) were provided to employees and "Q&A" sections were opened at the end of each meeting. This approach is part of communication activities adopted in RMS according to ISO 9001:2015 (ISO, 2018) and was continuously applied inside the company.

The RMC was also responsible for preparing the main standard operating procedure (SOP-RM 026 – Procedure for Risk and Opportunity Management), which described risk management activities, and with each new document, edition, or review, employees involved in the respective activity were trained again.

The processes flow mapping (Figure 1) was divided into Strategic Planning (Board of Directors), Technical Management (Technical Manager), Core Processes (Medical Director, Customer Service, Collection, Laboratory, and After Birth Service), and Support Processes (Quality Assurance, Purchasing, Marketing, Information Technology, Research and Development, Warehousing, Finance, and Human Resources).

Figure 1. Mapping of processes and sectors subdivided into strategic, technical, main, and support levels. Data collected by RMC at Cryopraxis® between May 2018 and May 2019.



Source: Authors.

The brainstorming meetings for risk identification resulted in 889 risks divided into 16 sectors. The percentage distribution of risks among the different sectors, before and after treatment, and the respective classifications (controlled, tolerable, and intolerable) are shown in Table 1. Additionally, the risks were divided according to the treatment strategy, discussed later in this session.

Table 1. Distribution and classification of risks by sector. The classification was based on criticality (controlled, tolerable, intolerable), treatment status (before, currently, and after), and risk control strategy (reduce, share, avoid and accept). Data collected by RMC at Cryopraxis® between May 2018 and May 2019.

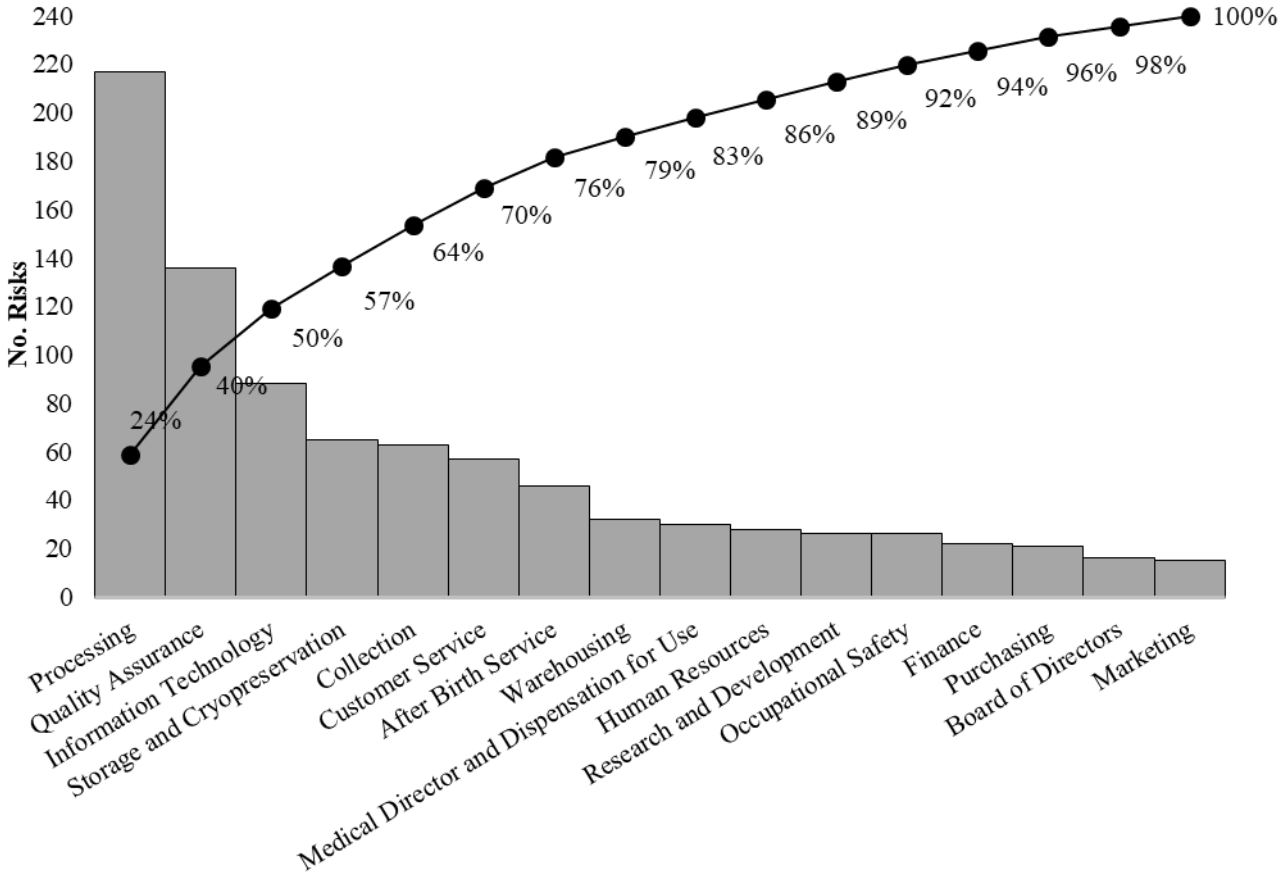
Sectors	No. risks	Risks before treatment (%)			Risks after or currently under treatment (%)					Risk control strategies after treatment (%)			
		Controlled[1]	Tolerable[2]	Intolerable[3]	Controlled[1]	Tolerable[2]	Intolerable[3]	Pending[4]	In process[5]	Reduce[6]	Share[7]	Avoid[8]	Accept[9]
Warehousing	32	37	63	0	100	0	0	0	0	3	0	84	13
Board of Directors	16	0	44	56	0	63	31	6	0	56	0	6	38
Customer Service	57	28	67	5	89	7	0	0	4	12	0	79	9
Storage and Cryopreservation	65	0	57	43	86	11	0	3	0	92	0	8	0
Collection	63	5	87	8	56	44	0	0	0	40	0	49	11
Purchasing	21	57	43	0	81	14	0	5	0	0	0	29	71
Human Resources	28	7	93	0	96	4	0	0	0	0	0	96	4
Medical Director and Dispensation for Use	30	77	23	0	100	0	0	0	0	0	0	80	20
After Birth Service	46	63	35	2	83	11	0	0	6	9	0	50	41
Finance	22	32	64	4	73	23	0	4	0	45	9	32	14
Quality Assurance	136	28	70	2	86	12	0	2	0	24	0	63	13
Marketing	16	75	25	0	100	0	0	0	0	25	0	50	25
Research and Development	26	4	65	31	42	58	0	0	0	54	0	19	27
Processing	217	1	46	53	87	13	0	0	0	100	0	0	0
Information Technology	88	27	59	14	56	39	1	4	0	18	0	59	23
Occupational Safety	26	77	23	0	88	12	0	0	0	96	0	4	0
Total	889	23	56	21	79	18	1	1	1	47	1	39	13

[1] Controlled risks = it is not necessary to adopt mitigating measures unless the risk can be further reduced with little cost and/or effort; [2] Tolerable risks = the company is prepared to deal with the risk. Actions are recommended to reduce the risk; [3] Intolerable risks = Operations under current conditions must be stopped until the risk is reduced to at least a tolerable level. These risks have priority for treatment; [4] risks for which treatment is still in the planning stage; [5] risks currently under treatment; [6] Reduce the impact of risk so that if it does occur, the problem it creates is smaller and easier to fix; [7] It is the sharing of risk with other stakeholders; [8] Avoid situations that potentially have a large negative impact on the organization; [9] Accept that it might happen and decide to deal with it if it does. Source: Authors.

Pareto distribution (Figure 2) shows a higher concentration of risks in the core processes, as exhibited in the mapping (Figure 1). Processing (24%), Cryopreservation and Storage (7%), Collection (7%), and Quality Assurance (15%) are sectors directly related to material handling, representing 481 risks or 54% of total risks.

The sectors with the lowest percentage of risks were Purchasing, Finance, Senior Management, and Marketing, as seen in Figure 2. This result denotes the presence of a greater number of risks in sectors related to the collection, maintenance, and management of biological material.

Figure 2. Pareto distribution of identified risks divided by sectors. Data collected by RMC at Cryopraxis® between May 2018 and May 2019.



Source: Authors.

The quality assurance sector interacts directly with all sectors of the company, while the other sectors are part of the production cycle, and although processing and storage are part of a macro-process that is the laboratory, each one of them has a type of technology, non-conformities or different conformances and specifications.

In the risk analysis, the classification of each one was defined through FMEA. The risk probability was ranked as follows: 1 (rarely, i.e. that risk may occur at some point), 2 (occasionally, i.e. the risk may occur at least once), 3 (frequently, i.e., may occur sometimes), and 4 (very frequently, the risk may occur most of the time), according to Table 2.

Table 2. Probability criteria for risk classification determined by RMC at Cryopraxis®

Level	Classification	Criteria
4	Very frequently	The event will occur most of the time, very high probability - 81% to 100%
3	Frequently	The event will occur frequently, high probability - 61% to 80%
2	Occasionally	The event is occasionally observed, of moderate probability - 41% to 60%
1	Rarely	The event is rare, low probability - 0% to 40%

Source: Authors.

Four qualitative ratings were determined for risk impact or severity, negligible (1), moderate (2), critical (3), and catastrophic (4) (Table 3). FMEA also determines that the criticality of failure modes must be calculated using the Risk Priority Number (RPN) (Najafpour, et al., 2017; Tague, 2005), multiplying probability and impact values (Table 4).

Table 3. Impact/severity criteria for risk classification determined by RMC at Cryopraxis®.

Level	Classification	Criteria
4	Catastrophic	Infeasibility of the objectives of the activity, processes, or business model. Failure to comply with laws or regulations that strongly harm the company's image and compliance. Fatality and/or destruction of the environment, facilities, or equipment. Loss of human life.
3	Critical	Strongly impacts activity objectives, processes, and business model. Failure to comply with laws or regulations that compromise the company's image. Fraud of any nature, regardless of the damage done. Damage to the physical integrity of persons.
2	Moderate	Difficulty in executing activities, processes, and the business model. Failure to comply with laws or regulations that do not compromise the company's image. Dissatisfaction and/or loss of customers.
1	Negligible	It can affect activities and processes, with an impact on efficiency, costs, and deadlines. It may have a slight effect on the achievement of business objectives.

Source: Authors.

Table 4. Risk Priority Number Matrix determined by RMC at Cryopraxis®.

Probability	Very frequently	**4**	**8**	**12**	**16**
	Frequently	**3**	**6**	**9**	**12**
	Occasionally	**2**	**4**	**6**	**8**
	Rarely	**1**	**2**	**3**	**4**
		Negligible	Moderate	Critical	Catastrophic
		Impact / Severity			

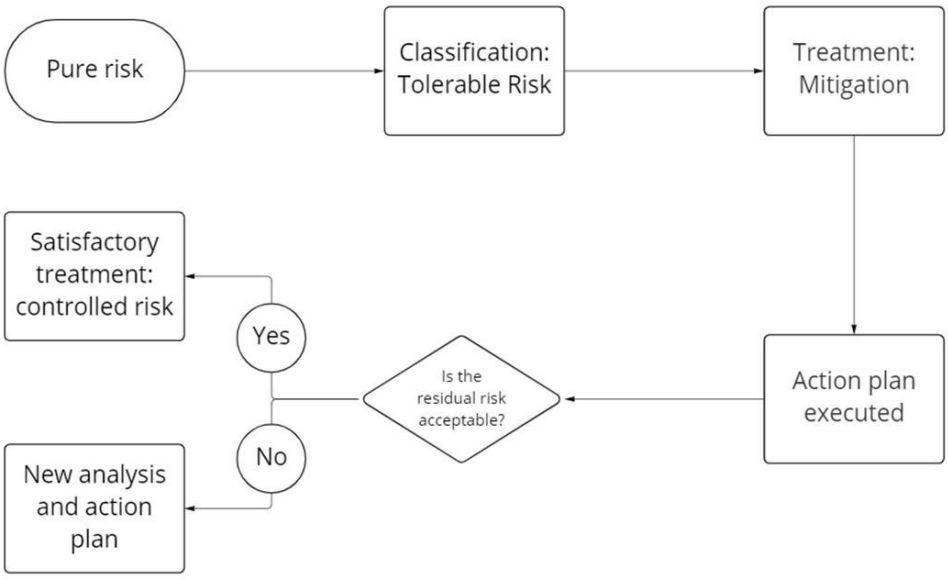
Source: Authors.

After an initial analysis, the RMC established the qualitative criteria for the treatment and control of risks, which were aligned with the RPN and the status classification as controlled, tolerable, and intolerable. Risks considered controlled should present RPN between 1 and 3 and mitigating measures were not necessary unless it was possible to reduce the risk with little cost and/or effort. In case of tolerable risks (RPN from 4 to 9) the organization should be prepared to bear it, but mitigating actions would be also recommended to reduce risks. Intolerable risks (RPN from 12 to 16) would require that operations must cease until the RPN reduction is at least to the tolerable level unless the board of directors assumes the risk. These risks would have priority treatment. The RMC evaluated the most appropriate option for the treatment of each risk taking into account the costs, implementation efforts, and benefits related to technical, regulatory, and environmental requirements, among others. After classifying the risks and their respective control strategies, the treatment approaches were defined. The first one was risk mitigation, aiming to reduce its probability of occurrence and impacts. A second way of dealing with risks was the sharing between two or more sectors of the company, dividing responsibilities, and increasing monitoring effectiveness. The third approach was to avoid the risk through effective elimination actions and, finally, control or accept the risk due to the impossibility of acting on its origin (Stamatis, 2003).

For each area, the RMC prepared action plans with definitions of tasks, responsible personnel, resources, and deadlines. The execution of the plans was controlled by the Quality Assurance sector. After implementing the actions and monitoring the results, the analysis and classification of residual risks were carried out. The risks that did not reach the acceptable level were reassessed by the RMC to verify the need to implement new actions.

The flowchart containing the recommended actions to mitigate pure risks classified as tolerable (RPN between 4 and 9) is shown in Figure 3. After the execution of the action plan, the residual risk must be evaluated and, if necessary, new measures must be taken to reach the controlled level.

Figure 3. Flowchart for mitigation of tolerable risks (RPN = 4 to 9) determined by RMC at Cryopraxis®.



Source: Authors.

The Processing sector showed 24% of all identified risks. Before treatment, many of those had a high level of intolerance, high probability, and high impact, as they could directly influence the quality of the biological material. A very representative example would be the risk of rupture of the blood bag sealing, which results in the loss of material. This pure risk, i.e., before the proposed treatment, had a probability of 3 (very frequently) and an impact of 4 (catastrophic) and may make it impossible to achieve the objectives of the activity, processes, or business model. As a result, actions were taken to mitigate the risk, such as hand-on training in the use of the sealing equipment and bag sealing process. Competence assessments in the admission of processing employees were also carried out during the first 3 months. Employees who successfully carried out the tasks during the first months were annually retrained on blood bag processing techniques and the checking of the sealer machine before starting the process. As a consequence, the residual risk, i.e. post-treatment, was classified as probability 1 (rarely) and the impact remained at the same level. The risk also changed from intolerable to tolerable. In this sector, the most frequent root cause was related to lack of attention of workers or absence of double-checking in critical steps of the process. Thus, as a preventive action, periodic training was carried out for employees, and at all critical stages, a double-checking process was adopted, so that these deviations are not observed throughout the process, resulting in an almost total reduction in the probability of occurrence of these risks.

The Processing sector already performed the risk management actions implemented in the previous ISO certification adequately, without the need to implement new routines. In the storage and collection sector, where 65 and 64 risks were identified, respectively, there was a change in 6% of the risk management actions, whose implementation was promoted at an interval above 6 months. On the other hand, 94% of the actions were already satisfactorily carried out by the organization in previous periods. In the Quality Assurance sector (136 identified risks), 23% of the planned risk management actions were new to the company. This occurred because the ISO standard changed requirements, requiring the implementation of new activities and procedures.

The risk management process is of great importance, as errors in the company's production cycle can lead to the loss of material, which has priceless value. The sectors and their interactions were mapped to identify the potential risks and their

importance at managerial and operational levels. This tool associated with Pareto distribution showed that sectors with activities that directly influenced product quality had a greater number of risks, such as processing, collection, storage, and quality assurance.

FMEA is described as an effective tool for analyzing and classifying blood bank processes since the quality of this material can be directly affected by multiple sources (Alcorta & Enrique, 2017; Lopez, et al., 2010). After FMEA, risks were classified as controlled (RPN = 1-3), tolerable (RPN = 4-9), or intolerable (RPN = 12-16) and, consequently, the risk control strategies were defined. FMEA data tabulation (Table 5) contributed to a better understanding of complex processes and their associated risks, allowing the elaboration of effective measures to reduce, share, avoid or accept risks (Stamatis, 2003).

Table 5. Failure Mode and Effect Analysis FMEA form template determined by RMC at Cryopraxis®.
*Criticality = controlled (RPN 1-3), tolerable (RPN 4-9) or intolerable (RPN 12-16).

FMEA Form

Date:
Process Description:
ID No.
Person in charge (data filling):

Process Function	Failure Mode	Effect of Failure Mode	Cause of Potential Failure Mode	**RPN**				**Control and Treatment**						**Residual Risk Analysis**				**Monitoring**		
				Probability (1-4)	Impact (1-4)	RPN value	Criticality	Recommended actions	Person in charge	Deadline	Resources	Implemented actions	Conclusions	Probability (1-4)	Impact (1-4)	RPN value	Criticality	Date	Situation after monitoring	Final comments

Source: Authors.

In most cases, residual risks were observed only with ongoing operations, which required prolonged analysis. The checks were carried out after FMEA and the probability and impact values were reevaluated after treatments. The last step in the risk management system involved the implementation of new protocols to eliminate or reduce residual risks.

Among 889 pure risks (before treatment) 23% were classified as controlled, 56% tolerable, and 21% intolerable, demonstrating a high share of tolerable and intolerable risks together, 77% of pure risks. However, after the implementation of treatment actions, residual risks showed a large number of controlled risks (79%) and a severe decrease in the share of tolerable (18%) and intolerable (1%). Only 2% of the risks are still pending or in process, that is, the treatment actions have not yet been initiated or completed due to the long time to reach the results. Overall, the proposed actions caused the controlled risks to increase by more than 3 times compared to the initial scenario, surpassing the sum of tolerable and intolerable risks. In the quality assurance sector, for example, 28% of pure risks were controlled, 70% tolerable and 2% intolerable. After the

treatment actions in this sector, the controlled ones increased to 86%, the tolerable ones to 12%, and intolerable residual risks no longer existed. All sectors, except the Board of Directors, had an increase in the percentage of controlled risks and a simultaneous decrease in intolerable risks (Table 1).

Risk monitoring is a process of observation and analysis continuously performed by Quality Assurance to identify changes in the probability and impact of risks over time. At this stage, the effectiveness of the action plans is evaluated and whether the residual risks correspond to the efforts employed in the treatment. In this work, the most used control strategy was mitigation (impact and probability reduction), followed by risk elimination/avoidance, corresponding to 47% and 39% of actions, respectively. Only 13% of the risks were classified as acceptable (under control), and only 1% (all from the Finance sector) were shared.

The present study proved to be challenging due to some peculiarities of the subject, due to the lack of current references and the need to pay to obtain access to the guides. There were also limitations imposed by the corporate environment and handling of confidential internal data. On the other hand, its development in a pioneering and prestigious company in the stem cell sector can be cited as strengths of the work. Additionally, this article demonstrates interesting data and a roadmap for all companies that need to implement risk management systems, which are rarely published. In this way, Cryopraxis proves to be at the forefront of quality assurance activities, serving as a reference for other umbilical cord blood cell storage companies.

4. Conclusion

The scientific literature on this topic is very scarce, with few published works with this approach to risk management system applied to cell therapy and UCBB. However, international authorities have seen risk management as an extremely important process for the development of new therapies. Despite the lack of requirement on risk management by many regulatory agencies for the areas of cell therapy and cell processing, it is possible to observe a growing implementation of Good Manufacturing Practices (GMP) for this type of activity. As an example, ANVISA published RDC 214/2018 which addresses the process of good cell and tissue practices, including risk management approaches. The biggest contributions of this work were the guarantee that the cellular products had the required quality for the intended use in humans and the implementation of the risk management culture at all hierarchical levels of the company, culminating in the ISO 9001:2015 certification and the AABB accreditation. This study will serve as a reference and guide not only for other companies that wish to implement a risk management system, but for Cryopraxis® itself in future audits, internal processes and training.

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Declaration of Interest Statement

The authors declare that there is no conflict of interest.

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