Research, Society and Development, v. 10, n. 7, e5010716144, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i7.16144

Systematic assessment of the drugs cold chain in Brazil by pharmaceutical professionals

Avaliação sistemática da cadeia fria de medicamentos no Brasil por profissionais farmacêuticos

Evaluación sistemática de la cadena de frío de medicamentos en Brasil por profesionales farmacêuticos

Recebido: 16/05/2021 | Revisado: 21/05/2021 | Aceito: 30/05/2021 | Publicado: 13/06/2021

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Abstract

One of the challenges in pharmaceutical logistics is to ensure that thermolabile drugs reach the patient with quality. This prospective cross-sectional study aimed to analyze the current cold chain scenario in Brazil. A semi-structured electronic questionnaire was applied for data collection. The total sample was 1793 pharmacists (CI: 99.998%; ME: 5%; p: 0.00002). 74.1% of the pharmacists reported that transportation is the most critical stage; 97.2% stated that the chosen mode influences the quality of the products; 52.5% reported only having partial parameters (tools) for the assessment of quality and that thermolabile medications possibly arrive altered to the final consumer due to the cold chain (59.8%); 66.9% do not have specific training on thermolabile medicines and 50.9% did not receive the technical data sheets of the products through the registration holders; 20.7% reported not being able to analyze or perform any activity related to qualification and validation. The absence of markings in the manual records (50.6%), the non-validation of the equipment used for conservation (30.6%) and the incorrect storage of medicines at domestic refrigerators (45.5%), near food (35.8%), were also noted. The non-measurement of the temperature of the products received was affirmed by 56.7%, as well as the use of thermometers to measure parameters (45.3%); 58.7% of the establishments do not have thermal mapping and 55.3% of the professionals are unaware of the thermal durability of the packaging. Due potentially

inadequate situation, there is urgency to implement tools that guarantee the quality of thermolabile drugs in all its logistical stages.
Keywords: Cold chain; Good manufacturing practices; Pharmacovigilance; Supply chain management.

Resumo

Um dos desafios da logística farmacêutica é garantir que os medicamentos termolábeis cheguem ao paciente com qualidade. Este estudo transversal prospectivo teve como objetivo analisar o cenário atual da cadeia fria no Brasil. Um questionário eletrônico semiestruturado foi aplicado para a coleta de dados. A amostra total foi de 1.793 farmacêuticos (IC: 99,998%; ME: 5%; p: 0,00002). 74,1% dos farmacêuticos relataram que o transporte é a etapa mais crítica; 97,2% afirmaram que a modalidade escolhida influencia na qualidade dos produtos; 52,5% relataram possuir apenas parâmetros parciais (instrumentos) para avaliação da qualidade e que os medicamentos termolábeis possivelmente chegam alterados ao consumidor final devido à cadeia fria (59,8%); 66,9% não possuem treinamento específico sobre medicamentos termolábeis e 50,9% não receberam as fichas técnicas dos produtos por meio dos titulares dos registros; 20,7% relataram não serem capazes de analisar ou realizar qualquer atividade relacionada à qualificação e validação. A ausência de marcação nos registros manuais (50,6%), a não validação dos equipamentos utilizados para conservação (30,6%) e o armazenamento incorreto de medicamentos em geladeiras domésticas (45,5%), próximo a alimentos (35,8%), também foi observado. A não medição da temperatura dos produtos recebidos foi afirmada por 56,7%, assim como o uso de termômetros para avaliação desse parâmetro (45,3%); 58,7% dos estabelecimentos não possuem mapeamento térmico e 55,3% dos profissionais desconhecem a durabilidade térmica das embalagens. Devido à situação potencialmente inadequada, é urgente implementar ferramentas que garantam a qualidade dos medicamentos termolábeis em todas as suas etapas logísticas.
Palavras-chave: Cadeia fria; Boas práticas de fabricação; Farmacovigilância; Gerenciamento da cadeia de suprimentos.

Resumen

Uno de los retos de la logística farmacéutica es conseguir que los fármacos termolábiles lleguen al paciente con calidad. Este estudio prospectivo transversal tuvo como objetivo analizar el escenario actual de la cadena fría en Brasil. Se aplicó un cuestionario electrónico semiestructurado para la recolección de datos. La muestra total fue de 1.793 farmacéuticos (IC: 99,998%; ME: 5%; p: 0,00002). El 74,1% de los farmacéuticos informó que el transporte es la etapa más crítica; El 97,2% afirmó que la modalidad elegida influye en la calidad de los productos; 52,5% refirió tener solo parámetros (instrumentos) parciales para la evaluación de la calidad y que posiblemente los medicamentos termolábiles lleguen alterados al consumidor final debido a la cadena fría (59,8%); El 66,9% no tenía formación específica en medicamentos termolábiles y el 50,9% no recibió las fichas técnicas de los productos a través de los registrantes; El 20,7% informó no poder analizar ni realizar ninguna actividad relacionada con la calificación y validación. La ausencia de marcado en los registros manuales (50,6%), la no validación de los equipos utilizados para la conservación (30,6%) y el almacenamiento incorrecto de medicamentos en refrigeradores domésticos (45,5%), cerca de alimentos (35,8%), también se observó. La no medición de la temperatura de los productos recibidos fue afirmada por 56,7%, así como el uso de termómetros para evaluar este parámetro (45,3%); El 58,7% de los establecimientos no dispone de cartografía térmica y el 55,3% de los profesionales desconoce la durabilidad térmica de los envases. Debido a la situación potencialmente inadecuada, es urgente implementar herramientas que garanticen la calidad de los medicamentos termolábiles en todas sus etapas logísticas.
Palabras clave: Cadena de frío; Buenas prácticas de fabricación; Farmacovigilancia; Gestión de la cadena de suministro.

1. **Introdution**

Thermolabile drugs are products that must be kept at a temperature between 2 °C and 8 °C, and must be monitored. Thermal traceability is necessary to ensure the therapeutic efficacy, quality and safety of finished products (Brazil, 2017c; Brazil, 2019b; Brazil, 2020a; Brazil, 2020b; Remor, 2016).

The transport stage is critical since, during the process, the quality of the drugs must be maintained, ensuring that the final product reaches the consumer with its physical and chemical properties unchanged. Therefore, transportation is currently one of the biggest challenges in the cold chain. The main factors that directly influence this stage are the choice of modal, that is, the type of transport chosen, the territorial extension of the route and the lack of training of the professionals involved. Aspects regarding the health control of medicines is also a worldwide problem (Brazil, 2017c; Cardoso, 2015; Costa et al., 2017; Freitas, 2013; Pereira et al., 2013; Remor, 2016; Sanches, 2007; Taylor, 2001.).

The literature reports that the failure of the cold chain has occurred due to the deficiency in the training of the employees involved, the application of an inadequate monitoring method, the incorrect use of tools, or the use of inappropriate equipment for measurement. Other factors are the absence of an assessment for the reintegration of thermolabile drugs exposed to a temperature excursion, as well as the absence of legislation with specific guidelines that impose continuous monitoring of products, ensuring the conservation of thermolabile products (Bogataj et al., 2015; Brown et al., 2016; Cardoso, 2015; Castro, 2019; Cattani, 2020; Cohen et al., 2007; Di Maio & da Silva, 2014; Ferraz, 2015; Fontelles, 2012; Freitas, 2013; Kartoglu & Milstien, 2014; Lavor et al., 2014; Lloyda et al., 2014; Luna et al., 2011; Lobera et al., 2014; Milstien, 2014; Ramírez et al., 2016; Ricote-Lobera et al., 2014.).

Tools such as standardization of processes, training and / or qualification of professionals through permanent education, monitoring and control of temperature in all logistical operations, the use of calibrated equipment for temperature measurement and the capacity of these equipments to record the thermal information, for example, is essential to guarantee the ideal conditions of medicines (Brazil, 2010a; Di Maio et al., 2014; Luna et al., 2007; Taylor, 2001).

Through this work, we can evaluate the landscape of the cold chain in Brazil, indicate points of improvement for the monitoring and control of thermolabile drugs, avoiding therapeutic inefficiency or the formation of toxic products from the temperature excursion. Through common sense, critical issues related to product quality could also be raised, such as access to technical information, training, current legislation, and the tools used to control and measure product conditions.

2. Material and Methods

This study was submitted to and approved by the Research Ethics Committee (CEP) on Human Beings, of the Federal University of Pernambuco (UFPE) in 2019, whose identification was CAAE: 04876818.2.0000.5208, following the guidelines of Resolution n. 466/2012 of the National Health Council (Brazil, 2013).

It was a prospective cross-sectional study, developed through a semi-structured questionnaire in an electronic format. In parallel, a systematic review was carried out on the main scientific databases such as the Virtual Health Library (VHL), Scielo, Pubmed and the CAPES Periodic Portal, seeking to respond directly and impartially to the objectives proposed between the years 1998 to 2020, due to the scarcity of published works related to the theme. For this survey, keywords such as "Medicines", "Stability", "Quality Assurance" and "Pharmaceutical Logistics" were used, as well as "Drugs", "Stability", "Quality Assurance" and "Pharmaceutical Logistics".

The survey was carried out for a period of 45 days, between the dates of October 28 and December 13 of 2019, with the link of the survey <http://bit.ly/2naVYdJPARAMETROS_DOS_MEDICAMENTOS_TERMOLABEIS> forwarded to pharmacists across the country, characterized as a nationwide campaign, which had the support of 12 Regional Pharmacy Councils and the Federal Pharmacy Council, enabling the dissemination of research through its media's platforms.

The questions elaborated sought to trace the sociodemographic profile, calculating the percentage frequencies and constructing the respective frequency distributions, as well as the frequency distributions of the questions related to the activities of professional practice, knowledge and access to information, professional routine, incidents were obtained quality and thermal qualification. To compare the prevalence found, the Chi-square test was applied to compare proportions, characterized as a quali-quantitative research.

It was defined as an inclusion criterion to be a pharmacist of both genders, in all areas of activity and who interact or who have already interacted with thermolabile drugs directly or indirectly. Pharmaceutical professionals not linked to the Regional Pharmacy Councils, who did not complete the survey completely and those who refused to sign the free and informed consent form, were considered exclusion criteria for the research.

For data analysis, the "Google Forms" database was converted into a Microsoft Excel spreadsheet, and later exported to SPSS software, version 18.

All information in this survey is confidential, with no volunteers identified and confidentiality about their participation ensured. The electronic questionnaire allows for indefinite custody, being mandatory maintained for at least 5 years.

For data analysis, the “Google Form” was transformed into a Microsoft Excel spreadsheet and later exported to SPSS software, version 18. For the analysis of the personal and professional profile of pharmacists, the activities of professional practice, knowledge and access to information, quality incidents and thermal qualification, the percentage frequencies were calculated by obtaining the frequency distributions of the related issues. To compare the prevalence found, the Chi-square test was applied to compare proportions.

This work was carried out with the support of the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Financing Code 001.

3. Results

In Brazil, as provided by the Federal Pharmacy Council in the 2019 elections, there were 231.767 eligible pharmacists. Within the survey cut off period, the link received 1817 responses to the study. Losses, that was, individuals outside the inclusion criteria were 0.45% (n = 8). In addition, 16 individuals refused to sign the consent form, totaling 0.89%.

Thus, it was possible to consider a sample of 1.793 pharmacists qualified for the present study, disseminated throughout the country (ME: 5%; CI: 99.998%; p: 0.002%). The categories or responses that presented a percentage below 1% were added.

In order to establish the sociodemographic profile of pharmacists, there was a higher prevalence of professionals working in the Southeast (57.0%), who identify themselves as female (72.1%), with postgraduate degrees at a specialization level (53.6%), graduated for more than 5 years (59.8%) and working in commercial pharmacy / community pharmacy (33.6%) (Table 1).

Table 1. Personal and professional profile of pharmacists who answered the questionnaire.

QUESTION ASSESSED	n	%
Q01 . Region		
North	46	2.6
North East	490	27.3
Midwest	112	6.2
Southeast	1021	57.0
South	124	6.9
Q02. Sex		
Male	501	27.9
Feminine	1291	72.0
Not binary	1	0.1
Q03. Education level		
University graduate	647	36.1
Specialization	961	53.6
Master's degree	154	8.6
Doctorate degree	23	1.3
Post doctoral	8	0.4
Q04. How many Yesrs have passed since the formation		
Just graduated	101	5.6
1 Yesr	125	7.0
2 Yesrs	167	9.3
3 Yesrs	123	6.9
4 Yesrs	100	5.6
5 Yesrs	105	5.8
Above 5 Yesrs	1072	59.8
Q05. Occupation area		
Commercial Pharmacy / Community Pharmacy	741	33.6
Public Pharmacy	319	14.4
Public hospital	252	11.4
Private Hospital	199	9.0
Distributor	178	8.1
Clinical, Toxicological Analysis, Laboratories in General	96	4.3
Shipping company	87	3.9
Industry	82	3.7
Magistral Pharmacy	80	3.6
Others*	177	8.0

Source: Research data.

By correlating the level of education and the time elapsed since graduation, it was possible to show that pharmacists seek training in postgraduate school only after the third year after training (54.5%). In this context, there is a higher prevalence of pharmacists graduated for more than 5 years, with postgraduate studies at a specialization level (62.8%) (Table 2).

Table 2. Distribution of educational level, according to the Yesrs that have passed since graduation.

Education Level	How many Yesrs have passed since your graduation?						
	Just graduated	**1 Yesr**	**2 Yesrs**	**3 Yesrs**	**4 Yesrs**	**5 Yesrs**	**Above 5 Yesrs**
University graduate	93 (92.1%)	99 (79.2%)	80 (47.9%)	45 (36.6%)	35 (35.0%)	29 (27.6%)	266 (24.8%)
Specialization	8 (7.9%)	25 (20.0%)	76 (45.5%)	67 (54.5%)	52 (52.0%)	60 (57.1%)	673 (62.8%)
Master's degree	0 (0.0%)	0 (0.0%)	10 (6.0%)	11 (8.9%)	11 (11.0%)	15 (14.3%)	107 (10.0%)
Doctorate degree	0 (0.0%)	1 (0.8%)	1 (0.6%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	19 (1.8%)
Post doctoral	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	7 (0.6%)

Source: Research data.

When raising the common sense of logistical issues according to the country's pharmacists, they reported that the most critical stage is transportation (74.1%), that the modal, that is, the way the thermolabile drugs moves influences the stability of the products (97.2%), that there are only partial parameters to analyze the products of the cold chain (52.5%) and that it is possible that are after passing through the cold chain, the products reach the final consumer altered, thus not maintaining the specifications provided by the manufacturer (59.8%) (Table 3).

Table 3. Common sense of pharmaceutical professionals.

Question assessed	**n**	**%**
Q06. Which stage of the logistical process do you consider most critical for the conservation of the temperature given by the manufacturer		
Transport	1328	74.1
Storage	190	10.6
Shipping / Dispensing	134	7.5
Distribution	61	3.4
Receivement	42	2.3
Separation	23	1.3
Other*	15	0.8
Q07. Believes that the type of modal (transport) influences the stability of the product		
Yes	1743	97.2
No	50	2.8
Q08. Do you believe that today there are parameters to analyze thermolabile drugs at any point in the cold chain?		
Partially	942	52.5
Yes	493	27.5
No	358	20.0
Q09. Do you believe that thermolabile drugs, after passing through the cold chain, arrive unchanged for the patient, thus maintaining the characteristics given by the manufacturer		
Yes	721	40.2
No	1072	59.8

Source: Research data.

Pharmacists reported not having received specific training on thermolabile drugs (66.9%). Only 27.9% of them were assertive when they reported that Brazil is classified as Climate Zone IV - Hot and humid, warned not to receive the technical data sheets of the products (50.9%) and were informed to update themselves on the issue of medicines thermolabile using data spreadsheets. Technical legislation (37.8%) and current legislation (35.0%) (Table 4).

Table 4. Distribution of knowledge and access to information of the evaluated pharmacists.

Question assessed	n	%
Q10. Have you received any specific training related to thermolabile products		
Yes	593	33.1
No	1200	66.9
Q11. Knows inform, according to ANVISA (National Health Surveillance Agency) which climate zone in which Brazil is		
I don't know how to inform	601	33.5
Climate zone I - Temperate	123	6.9
Climate zone II - Subtropical	460	25.7
Climate zone III - Hot and dry	108	6.0
Climate zone IV - Hot and humid	501	27.9
Q12. The technical data sheet of the product is made available by the industry to the technicians in charge of the product so that they can consult in case of any problem		
Yes	672	37.5
No	912	50.9
Not applicable	209	11.7
Q13. Which tool do you use the most to keep up to date on the "Thermolabile Products" theme?		
Product Technical Sheets	678	37.8
Current legislation	627	35.0
Article (s)	317	17.7
Internet	43	2.4
Degradation studies	33	1.8
Books	33	1.8
Large circulation newspapers	18	1.0
Others*	44	2.5

Source: Research data.

Among the processes presented, there is a higher prevalence of pharmacists capable of analyzing technical reports issued in a qualification (24.1%). Then came the professionals who declared themselves able to perform the thermal mapping of the environment (22.7%) and in the third highest prevalence, are the pharmacists who said they did not have knowledge to perform any of the processes presented (20.7%) (Table 5).

Table 5. Distribution of the professionals' perception about the activity capacity.

Question assessed	n	%
Q14. Do you think you are able to		
Conduct packaging qualification	436	15.1
Perform thermal mapping of the environment	634	22.0
Perform equipment qualification / validation	369	12.8
To analyze the technical reports issued from a validation	695	24.1
Does not have the knowledge to carry out any of the aforementioned processes	599	20.7
Never heard of these processes	147	5.1
Other	8	0.2

Source: Research data.

As for the tools used and their efficiency, 50.6% of pharmacists reported that there are defaults in the manual quality records and 30.6% reported that the equipment used for the conservation of medicines is not qualified. In addition, respondents were able to identify products on the door of the domestic refrigerators or in the containment drawer (45.5%) and foreign objects such as water bottles, foods in general, among other things, together with the products (35.8%). In addition, 38.9% of pharmaceutical professionals stated that they had no knowledge of the changing conditioning thermal battery processes during transport, and that upon receipt, thermolabile drugs are not fully measured (56.7%) (Table 6).

Table 6. Distribution of questions related to the routine of the evaluated pharmacists.

Question assessed	Reply		
	Yes	**No**	**Not applicable**
Q15. In the case of manual recording of measurements, there is (are) no appointment (s) at any of the times established for the measurement of temperature by the responsible employee	908 (50.6%)	714 (39.8%)	171 (9.5%)
Q16. The equipment used by the company you work for or have worked for has been qualified	1061 (59.2%)	548 (30.6%)	184 (10.3%)
Q 17 . In the case of the use of domestic refrigerators, has it been seen, or there have been reports of visualization of the packaging of products on the refrigerator door, in the containment drawer or in some place	815 (45.5%)	671 (37.4%)	307 (17.1%)
Q18 . As for the equipment, it has already been viewed, or there have been reports of viewing the guarding of foreign objects (water bottle, food in general, among other things) with the products	642 (35.8%)	1059 (59.1%)	91 (5.1%)
Q 19 . It is known to change the batteries or some material for the conservation of the temperature (Ex .: ice, dry ice, thermal blankets, others) during the transport of the thermolabile product	959 (53.5%)	698 (38.9%)	136 (7.6%)
Q20 . The temperature of 100% of the thermolabile products received is checked	641 (35.8%)	1017 (56.7%)	135 (7.5%)

Source: Research data.

Even when asked about their routine, according to the respondents, 41.1% of the companies that invest in improvement projects have already stopped investing because they were based on good practices and not on the current legislation (41.1%) (Table 7).

Table 7. Distribution of questions related to the routine of the evaluated pharmacists.

Question assessed	Reply			
	Yes	**No**	**Not applicable**	**p -value[1]**
Q21 . The company you work or worked with has already stopped investing in a project because it is not a legal requirement but an improvement based on Good Practices (GP)	354 (41.1%)	507 (58.9%)	-	<0.002%

Legend: [1]p-value of the Chi-square test for comparison of proportions.
- There were no observations.

Source: Research data.

As for the equipment used for temperature monitoring, the highest prevalence was the use of thermometers (45.3%) and thermo-hygrometers (37.4%). As for medication storage equipment, the most used was the domestic refrigerator (68.7%) (Table 8).

Table 8. Distribution of questions related to the routine of the evaluated pharmacists.

Question assessed	n	%
Q22 . What equipment is used to measure the temperature?		
Thermometer	813	45.3
Thermohygrometer	670	37.4
Thermometer / Thermohygrometer	128	7.1
Datalogger	60	3.3
Thermometer, Thermohygrometer , Datalogger	36	2.0
Thermohygrometer , Datalogger	21	1.2
Thermometer, Datalogger	19	1.1
Others*	46	2.6
Q23 . Indicate the equipment that the company you work or worked with has for the conservation of thermolabile products within the ideal temperature range given by the manufacturer.		
Fridge	1232	68.7
Cold chamber	194	10.8
Refrigerator, Cold room	90	5.0
Refrigerator, Freezers	68	3.8
Not applicable	60	3.3
Refrigerator, Cold room, Freezers	35	2.0
Freezers	32	1.8
Cold room, Freezers	19	1.1
Others*	63	5.5

Source: Research data.

There are no complaints related to temperature excursions at the time of receipt of the products (60.6%), technical analysis of the products that underwent an excursion (56.6%), or even the registration or forwarding of non-conformity reports linked to incidents (57.8%) (Table 9).

Table 9. Distribution of incidents of quality and thermal qualification cited by the evaluated pharmacists.

Question assessed	Reply		
	Yes	No	Not applicable
Q24. There are records of customer complaints, or you have already registered a complaint, regarding products because they are not within the ideal temperature .	592 (33.0%)	1087 (60.6%)	114 (6.4%)
Q25. In the case of excursions, that is, extrapolation of the ideal temperature, whether positively or negatively, there is some technical analysis based on the stability of the product to reintegrate it into the stock or discard it	527 (29.4%)	1015 (56.6%)	251 (14.0%)
Q26. In the case of excursions, that is, extrapolation of the ideal temperature, either positively or negatively, at any stage of the process, a report is issued , informing that the product reintegrated into the stock has been exposed to a temperature excursion for a certain period, and this report is directed to the recipient	367 (20.5%)	1036 (57.8%)	390 (21.8%)
Q27. Did the company you work promote a thermal mapping for placing the temperature measurement equipment at the positive and negative critical points?	532 (29.7%)	1053 (58.7%)	208 (11.6%)
Q28. You are aware of the thermal durability of the packaging used to send / receive the thermo-labile products	711 (39.7%)	991 (55.3%)	91 (5.1%)

Source: Research data.

The establishments do not have thermal mapping and do not know how to inform the critical points (58.7%) or the thermal durability of the packages they send or receive through the cold chain (55.3%) (Table 09).

Finally, it was possible to see that only 3.9% of pharmacists participated in Public Consultation (CP) 343, May 11, 2017. CP is one of the tools used by the National Health Surveillance Agency, in order to seek popular participation, before to change a legal guideline.

As for the respondents who reported having directed their contributions, 62.9% were able to view them in the Resolution of the Collegiate Board (Table 10).

Table 10. Distribution of the professional experience activities of the evaluated pharmacists.

Question assessed	n	%
Q29. You participated in the construction / drafting of the Resolution of the Collegiate Board (RDC) 304, of September 17, 2019, through Public Consultation (CP) 343, May 11, 2017		
Yes	70	3.9
No	1454	81.1
Not applicable	269	15.0
Q30. His contribution in Public Consultation 343, of May 11, 2017, was accepted, that is, it was inserted in the Resolution of the Collegiate Board (RDC) 304, of September 17, 2019		
Yes	44	62.9
No	12	17.1
Applicable	14	20.0

Legend: [1]p-value of the Chi-square test for comparison of proportions.
* Added categories that presented a percentage below 1%.
Source: Research data.

4. Discussion

Control, verification and conservation actions are essential for the conservation of thermolabile medicines, and must extend throughout the logistical flow, ensuring that the products are administered by the patient under the same conditions as the products were manufactured. The scarcity of information led to the survey of actions and points of verification routinely experienced by pharmacists in all areas that may directly or indirectly impact the quality of medicines.

As for the characterization of the research participants, according to the survey carried out by the International Pharmaceutical Federation (FIP), between the years 2015 to 2017, which involved 74 participating countries and territories, there are 4.067.718 licensed or registered pharmacists, but only 2,824,984 professionals carry out their activities (Fip, 2017). Still through surveys aimed at pharmacists by CFF and FIP, it was possible to perceive a higher prevalence of females, both nationally and worldwide, being represented by 57% of the participating individuals, corroborating the data of the present study (Brazil, 2015; Fip, 2017).

The quantitative results exposed in the research are consistent with the survey published by the Federal Pharmacy Council in 2018, configuring the Southeast region as the most populous in relation to the number of professionals in Brazil (Brazil, 2018b).

When it comes to the area of activity (Table 1), when a higher prevalence of professionals working in pharmacies and drugstores was seen, the data in the present study are in line with the FIP data, since 58 (86%) of the countries / territories research participants recorded such prevalence (Fip, 2017).

In the case of training after graduation, the data from the present research reported a higher prevalence for latu sensu courses, since there is a greater number of courses offered, in addition to professionals looking for content that is more and more suited to their professional practices. (Brazil, 2015).

These data corroborate the information from the CFF, when 80.8% of the professionals reported a preference for specialization, as well as being in line with the return provided by the pharmacists participating in the research (Brazil, 2015).

Brown et al. (2017) makes evident the concern regarding the offer of training courses focused on pharmaceutical

logistics, making global influences responsible, so that they can prepare and develop professionals capable of making decisions, through a systematic methodology (Table 2).

According to the WHO, transport conditions have been inadequate for the handling of thermolabile products for decades, and this stage has been indicated as critical by several authors (Brazil, 2017c; Cardoso 2015; Di Maio et al., 2014; Freitas, 2013; Taylor, 2001; Sanches et. al., 2007; Who, 1988).

All professionals, including those who handle the medication, must also be trained to transport it within the ideal temperature and handle the gauging equipment using them appropriately. The equipment must be able to provide data to demonstrate thermal compliance throughout the movement (Who, 2014).

The use of continuous monitoring equipment has been shown to be effective in preventing temperature and humidity excursions, with emphasis on real-time monitoring systems, as they enable immediate corrective actions (Lloyd et al., 2015).

The way in which thermolabile drugs are transported must ensure the quality of the products (Brazil, 2017c). Planning for moving products is essential. Only by developing strategies with the use of appropriate tools will it be possible to maintain the ideal conditions of the products throughout the route.

For the correct use of tools such as qualified passive packaging, it therefore needs to know at least their capacity and thermal durability. The information regarding the date and time that were sealed must still appear on the outside of the packaging. These are Good Practice measures and should be known to everyone involved.

Collegiate Board Resolution (CBR) No. 430/2020 reports that the products must be received inside the cold chamber, or close to it, in an area called anteroom, and the entire excursion time must be recorded, however in this there is no information regarding the separation of these products. Following this same reasoning, it is also known that the products must be separated in controlled temperature areas, taking into account also the record of all excursion temperatures to which the products were exposed, since these exposures are cumulative (Brazil, 2020c; Who, 1988).

It is great to note that the cold chain must encompass all processes and ensure, through records, a temperature between 2 to 8 ° C. In complex operations involving several modes, the qualification of transport systems is essential, aiming to ensure product quality, and to reduce the possibility of temperature excursions (Brazil, 2017c).

Therefore, the existence of partial parameters, informed by more than half of the pharmacists, is not sufficient to guarantee the quality of the drugs, as they only make it possible to show part of the processes, as opposed to the definition of the cold chain, which are processes that must maintain the ideal temperature conditions, preserving the ideal conditions of the products, from the moment of their manufacture, until their administration to the patient (Ramírez et al., 2016).

In line with this statement, in 2014 in Madrid, Spain, in a published work related to vaccine transport, it was found that 64.6% ($n = 417$; 95% CI; $p < 0.001$) of pharmacists did not have tools that could ensure the conservation of thermolabile drugs in cold chain processes (Ricote-Lobera et al., 2014).

Through this work, we can evidence that more than half of the pharmacists (59.8%) informed that the drugs arrive altered in the patient, which are potentially dangerous and may result in therapeutic ineffectiveness, or even be exposed to toxic substances formed by the degradation caused by thermal instability.

RE No. 679/2019, of the Federal Pharmacy Council, is clear about the duties of pharmacists in the logistical scope, stating that this professional must manage, guide and organize all the processes involved in the logistical steps. With regard to the cold chain, the professional must develop and conduct the thermal qualification program for the tools, equipment and processes used, basing their actions on guides, regulations and legislation in force (Brazil, 2020a).

This resolution also establishes that the temperatures of the processes involved must be monitored and recorded, qualify the product handling routes and conduct training for all professionals involved. In the indication of any incident, diversion or

excursion in any logistical stage, the pharmacist must contact the manufacturer, consenting bodies, companies involved in the process so that corrective measures can be adopted (Brazil, 2020a).

Therefore, starting from these impositions punctuated by the CFF, in the face of any situation that is potentially harmful to life, the pharmacist must interfere, promoting continuous improvement actions, since it is his responsibility to use tools that can evidence thermal compliance maintaining the quality of medicines (Brazil, 2020a).

An overview of the public sector's storage conditions could be obtained through state reports prepared after inspections by the Federal Comptroller General. The reports showed that eleven are the states whose storage conditions have been shown to be inadequate. Among the irregularities, the ineffectiveness of the pest control, the presence of mold caused by infiltration in the structure, volumes of medicines against the ceiling, wall or stored directly on the floor, the incidence of sunlight, temperature and high humidity in the storage environments were described, among others. Studies related to the qualification of pharmaceutical services in Brazil, also describe the inadequacy in the storage of medicines in 39% of the 597 municipalities audited (Brazil, 2016; Brazil, 2017a; Brazil, 2017b; Brazil, 2017f; Brazil, 2017g; Brazil, 2017h; Brazil, 2017i; Brazil, 2017j; Brazil, 2017k; Brazil, 2017l; Brazil, 2017m; Costa et al., 2017; Vieira, 2008).

These conditions show the dangerous potential turned to the conditions of the products annulled by the National Health Surveillance Agency, being aligned with the absence of parameters or even that the thermolabile drugs are possibly not arriving in the same conditions as they were manufactured.

Still regarding this theme, Rodrigues et al. (2017) place emphasis on the lack of structural aspects, such as inadequate walls, floors and ceilings, is indicative of poor sanitary conditions for the storage of medicines. The weakness of aspects such as human resources, connectivity, furniture, among other things, could still be evidenced in this study. He highlights through the analysis of the Structural Axes of the National Pharmaceutical Assistance Qualification Program carried out in 316 municipalities that 44% of the structures were classified as unsatisfactory and 21% of them as critical, proving to be inadequate for the storage of medicines and health products (Rodrigues et al., 2017).

Regarding thermolabile drugs, it was possible to see non-conformities in the state reports of the states of Amapá, Bahia, Mato Grosso do Sul, Rio Grande do Norte, Brasília and six others. Non-conformities such as pointing out temperature excursions, products stored inside the conditioning equipment in plastic or cardboard packaging, prevented thermal convection, freezer overcrowding and cold chambers, problems in the electrical networks causing the temperature excursion, problems in the thermal conditioning equipment, disorganization of the products inside, hinders the air flow between the products and the physical counting of the medications, in addition to losses of products due to expiration or damage, lack of conservation equipment or conservation equipment in insufficient quantity and the non-existence of the system of alarm (Brazil, 2016; Brazil, 2017f; Brazil, 2017g; Brazil, 2017h; Brazil, 2017j).

It is important to emphasize that the inadequate administration of the storage conditions of the thermolabile causes losses due to expiration, or due to damage due to the poor packaging of the drugs, in addition to the inefficiency of public policy. This disposal could be seen in 11 states (BBrazil, 2017d). Media articles demonstrate the continuity in the irregularities pointed out. In October 2018, in a batch of vaccines from the Ministry of Health (MS) transported from Rio de Janeiro to São Paulo and monetized in R $ 14,814,812.27 (Fourteen million, eight hundred and fourteen thousand, eight hundred and twelve reais and twenty seven cents), a negative excursion was found, that is, the truck left Rio de Janeiro with temperatures below 0 ° C. The Public Defender's Office of the Union (DPU) of the state of Rio de Janeiro reported that the São Paulo State Department of Health refused to receive the 280 volumes. Through the report, it was not possible to evidence whether the disposal was total or partial (Saringer, 2018).

In June 2019, 7,149 units were discarded after a complaint in the city of Nova Friburgo, due to problems with refrigeration equipment, and a deadline for resolution was not determined by the Secretariat for Health Surveillance. The interruption of influenza vaccination for lack of vaccines has been reported (News - G1, 2019).

Reports in Blumenau, in the year 2019, find problems in the vaccine refrigeration equipment, in the Old Central neighborhood, impacting the provision of the vaccination service. In addition to the breakage of the equipment, the type of equipment, the domestic refrigerator, is not recommended, or currently allowed, by the MS (Cattani, 2019).

This situation could be observed in at least 5 (five) other health centers, with concern about thermal monitoring being reported by one of the employees, as he knows that the equipment is not ideal for the storage of medicines, considering the fact as a risk to the patient. This report also reports the loss of part of the product lots due to equipment (Brazil, 2017n; Cattani, 2019).

The issues surrounding the health conditions of medicines within the scope of private companies could not be addressed due to the insufficient material related to the topic addressed. Through an analogy based on research, in which pharmacists affirmed that thermolabile medicines do not reach the patient unchanged and in this brief overview of public health, the quality of the products is of concern, and these are potentially harmful (Table 3).

Knowledge is the greatest tool for maintaining product quality, not only for pharmacists, but for everyone involved in the processes that have an impact on the ideal characteristics of thermolabile medicines, as well as on the availability of information relevant to each medicine, extremely relevant to establish the ideal conditions for storage, transport and dispensing, in order to avoid quality incidents (Brazil, 2010a; Di Maio et al., 2014; Kartoglu & Milstien, 2014; Loberal et al., 2014; Luna et al., 2011; Remor, 2016; Sanches et al., 2007; Silva et al., 2012).

Thus, themes such as maintaining the ideal conditions of thermolabile drugs and knowledge about stability and carrying out continuous training, in order to familiarize the professional with the products and processes are considered of the utmost importance by WHO (Who, 1988) .

The registration holder and all companies belonging to the cold chain are jointly responsible for the quality of the product and must ensure continuous training so that everyone involved becomes familiar with all the particularities (Brazil, 2019a; Brazil, 2020c; Who, 1988).

According to CBR No. 301/2019, the registration holder must provide training for all professionals in the manufacturing stages and also for professionals who can directly impact on maintaining quality, leading to the discussion of everything that may be relevant throughout the quality system and its guidelines (Brazil, 2019a).

In contrast, it was evident that, in most supply chains, there are no employees exclusively dedicated to logistical management, and what is seen is a team without training in the logistical chain, often with the development of assignments. Already expanded, and without data support to support decisions in factual ways (Brooks et al., 2017).

In this sense, several deepening programs have emerged globally, developing trained professionals for the management of health logistics, also known as pharmaceutical logistics, with the greatest challenge being the application of control tools within the context of each region. In addition to these training programs, undergraduate and graduate courses also appear to grow exponentially in countries that need this demand, such as Egypt, Africa, Ghana, among others (Brown et al., 2017).

One of the reasons for the growth of the courses is the absence of trained professionals, which are essential to develop them through continuous experience, often in partnership with the private sector (Brooks et al., 2017).

As for the Climate Zone (ZC), according to WHO, Brazil follows the parameters of ZC IVb, thus, the limit of temperature and relative humidity that must be maintained is 30 °C and 75% respectively (Who, 2009).

In this context, there is very strong evidence that professionals do not know what the ideal temperature for packaging products are based on, considering the significant prevalence of pharmacists who reported not knowing (33.5%) and

professionals who are assertive about ZC IV (27.9%). A tool that can be used to work on the analysis of medications on excursions, or those that have been exposed to accidental cold chain failures are contingency protocols, which enable quick access to medication information, preventing damage to the patient and reducing the financial impact from disposal (Parraga et al., 2011; Ricote-Lobera et al, 2014).

For the elaboration of this protocol, the drugs conditioned to the temperature range of 2 °C and 8 °C must be raised, and from this, seek information from the manufacturers regarding the stability of the products, being essential the technical sheet, or even the conservation guides for this analysis that will support the procedures for each medication (Parraga et al., 2011; Ricote-Lobera et al., 2014).

Concerning and contradictory are the statements of the professionals who participated in the research when they claim to update themselves on the topic of thermolabile drugs through the technical data sheets of the products (37.8%) and the current legislation (35.0%), and it can also be seen through the affirmations that 59.9% of the professionals do not have access to the technical files and the current legislation focused on the Good Practices of Storage, Distribution and Transport, is being partially implemented after 23 years of delay (Brazil, 1999; Brazil, 2020c).

In line with these points, the biggest difficulty, according to Ricote-Lobera et al., 2014, is to collect this information. In his work, he disclosed that only 17.7% of the information could be collected through the conservation guides, with 82.3% remaining to be collected by the registry holders. He also informed that 3.5% of requests were not met, and 40.7% of those who returned, reported that if there is an accidental failure in the cold chain, contact should be made, thus not making available the product stability study. Through this survey, Ricote-Lobera et al., 2014 also reported that it is not possible to obtain concrete data regarding the stability of products (Ricote-Lobera et al., 2014).

Cohen et al. (2007) reports that data collection, regarding product stability, was still hampered by the long response time and the unavailability of information, which according to the manufacturer, could not be provided due to legal issues.

The above statements could be confirmed through this work, where 59.9% of pharmacists say they do not have access to the technical data sheets of the products. Access to information must be guaranteed at all stages of the operational flow, so that ideal conditions are maintained, ensuring the universal right to information, and that this data is made available through product registration with the National Health Surveillance Agency. It is worth mentioning, just as the authors recorded in their work, that the cold chain must maintain ideal conditions according to the information given by the manufacturer and this data should only be used in accidental excursions (Parraga et al., 2011; Ricote-Lobera et al., 2014) (Table 4).

Turning to this theme, it can still be seen in the CFF survey, done in 2015, that the technical data sheet of the products does not appear in the list of options selected by pharmacists. In 2015, in the survey of the CFF, the technical data sheet of the products or the current legislation does not appear as one of the selected options (Table 11). Given the above, it is significant to highlight that the pharmacist must be trained in order to analyze the reports of all processes. This knowledge will allow this professional to relate everyday facts and suggest improvements, as well as to argue, through evidence, the quality incidents that may arise (Table 5).

Table 11. Sources of consultation.

Dictionary of Pharmaceutical Specialties (DEF)	60.9%
General Internet	55.9%
Internet databases	54.8%
Remedy Guides	47.6%
Goosman & Gilman - The Pharmacological Basis of Therapeutics	27.5%
Vade Mecum	26.9%
Pharmacy Guide	20.5%
Guanabara Therapeutic Dictionary	20.2%
Clinical Pharmaceutical Portal	18.5%
Evidence-Based Health Portal	15.9%
Pharmacopoeia	13.7%
Others	8.6%
Martindale - The Extra Pharmacopoeia	6.1%

Source: Brazil (2015).

Failure to comply with the procedures, such as the absence of records in manual markings, products stored in the refrigerator doors or in the containment drawer and the storage of food or drinks in the equipment that packages the products are factors that damage the quality, safety and effectiveness of the products.

It is very important to point out that all processes that directly and indirectly impact the quality of products must be written in detail through standard operating procedures in order to standardize temperature control through thermal monitoring throughout the logistical flow, including indicating the mandatory calibration of equipment, the use of equipment that allows the extraction of electronic records and through the thermal qualification of the environment, the indication of the points to be thermally monitored (Brazil, 2010a; Brazil, 2019; Brazil, 2020c; Cardoso, 2015; Freitas, 2013; Remor, 2016;Taylor, 2001) (Table 6).

The absence of manual markings indicates a failure in thermal monitoring, and may omit temperature excursions. In Santa Catarina, the thermal conditioning of the refrigerators was not seen as reliable and due to this fact, the manual monitoring records were not being filled out. This lack of evidence generates distrust in the control of ideal conditions for the maintenance of medicines (Brazil, 2017l).

Furthermore, manual notes are not indicated in compliance with good distribution standards, which require that they be performed automatically and electronically.

When using domestic refrigerators to store thermolabile products, storage in the door and / or containment drawer, can expose the product to a positive and negative excursion, respectively. These incidents were reported in 1988 and remains to a 14% incidence of food in the cold rooms and refrigerators of health establishments in the Metropolitan Region of Recife (Who, 1988).

The storage of food and beverages in the equipment that stores the medications can cause contamination of both the medications and of the foods and beverages, highlighting, above all, that some of these medications have pathogens, in the case of some vaccines. CBR No. 430 in the section related to qualifications and validations makes it clear as to the mandatory qualification and validation of computerized equipment and systems before their use or after significant changes, as well as making clear the responsibility of Quality Management in conducting these actions (Brazil, 2020c).

Thermal qualification is necessary to prove the thermal stability of the equipment, to know the critical points at which the highest and lowest temperatures can be reached and to evidence whether the equipment or the environment is capable of guaranteeing the ideal temperature of the medicines. The exchange of thermal conditions in qualified packaging was the subject of discussion in which it was regulated that the exchange of thermal conditions is not considered a violation of thermal packaging (Brazil, 2019b; Brazil, 2020b).

It is needed that a procedure is established for the exchange, for the execution and for the registration of the execution of this process, training the professionals involved so that it can be fulfilled, especially when the transportation stage is outsourced. This procedure should score the thermal durability of the qualified volumes, the configuration of the conditioning material inside the packages. Thermal monitoring is the main tool to guarantee the quality, safety and efficacy of the products handled, stored and distributed, only in this way, is it possible to highlight the exponential risks in the processes, and to develop improvements based on the recorded facts. Upon receipt of the thermolabile medicines, the storage and transport conditions must be checked, the product identification characteristics checked, and the temperature checked at the time of receipt, confirming that the temperature is correct, and should direct the non-compliant products to the quarantine area, so that they can be investigated, documenting all actions (Bogataj et al., 2015; Who, 2011) (Table 6).

Strategic management tools are being increasingly used for Risk Management, as established in CBR No. 430 (Brazil, 2020c), as is the case with Total Quality Management used to optimize quality, productivity, profitability, among other things. This dedicates total satisfaction to the customer, through the continuous improvement of the processes and the continuous effectiveness and efficiency of the company, involving all professionals and reinforcing an integrated, prospective and consistent system (Hallem et al., 2015).

According to Haleem et al. (2015), all processes and products have risk elements, which must be scored in the risk management plan. Quality Risk Management can be used to analyze, ensure, communicate and review the risks inherent in the quality of medicines during their entire useful life, and changes can occur in any process.

Risk analysis and management support factual decisions based on data. Through this, one must identify the risk and assess its critical and direct actions, so that those responsible can prioritize them (Kartoglu & Milstien, 2014).

The survey and treatment of corrective and preventive actions, in addition to being a legal requirement, is a necessary tool. Companies should focus on correcting and preventing problems, and prevention is, in most cases, cheaper economically than corrective actions and view nonconformities as an opportunity for improvement (Brazil, 2020c; Hallem et al., 2015).

The tools in general are intended to mitigate risks and develop continuous improvement projects to maintain the quality of products and processes. It should be noted that the maintenance of all processes has a direct impact on the health of individuals (Table 7).

It is often considered the need to record the temperature using thermometers at least twice a day in manual records. These records only capture the moment's record, not being adequate, as they interpret the general situation by momentary measurements, and may mistakenly deduce that there was no temperature excursion in the intervals of the measurements (Bogataj et al., 2015; Lloyda et al., 2014).

In a 30-day study, it was observed that electronic monitors capable of storing information were superior when compared to thermometers, which were not able to record most of the excursions. There is a strong recommendation for abandoning thermometers in thermal monitoring, as it has not been shown to be effective, against excursions that can be harmful to thermolabile drugs (Bogataj et al., 2015; Kartoglu & Milstien, 2014; Lloyda et al., 2014).

Another serious fact is that only the temperature can be measured through thermometers, and relative humidity is no longer measured. These two parameters are imposed through legal guidelines and must be complied with (Brazil, 1999; Brazil, 2020c)

In addition, in several situations in the literature, the absence of equipment for measuring environmental parameters in refrigerators for the storage of temperature-sensitive drugs has been reported (Brazil, 2016). For the movement of medicines, several technologies are already available for monitoring thermal traceability (Taylor, 2001).

Such instruments as the “Radio-Frequency Identification” (RFID) which are electronic meters connected to a network that allows the transmission of information from the chip to a reader, through the conversion of radio waves into digital

information. The information is transferred to a computer that emits a thermal report of the route traveled in real time, allowing the professionals involved monitoring the data received and in the case of temperature excursions, respond promptly through corrective factual actions (Freitas, 2013; Lloyda, et al., 2014; Spagnol et al., 2018).

Chemical monitors have the main characteristic of changing the color or the appearance of the indicator. This has as a disadvantage the absence of thermal monitoring during movement, as it does not present the history of the temperature at which the drugs were exposed, but only the suitability or not of the pharmaceutical product (Brazil, 2017c; Freitas, 2013; Pereira et al., 2013; Remor, 2016;).

The electronic temperature indicators are only able to inform if the products or volume were transported or not, at the temperature indicated by the manufacturers, informed by an "X", for example, if it has been exposed to inadequate temperatures. The records informed through these devices can be irreversible, having as a disadvantage the fact that they are disposable (Who, 2014).

In this same technological bias, there are Dataloggers, which are electronic data record monitors capable of storing the thermal traceability of products during the movement process and connected to software, enabling the issuing of product movement reports, which guarantees the evidence of thermal compliance during the process in compliance with regulations. Also known as electronic data record monitors, they are used to monitoring environments. Some models are able to emit a light alert in the event of an excursion (Brazil, 2017c; Di Maio et al, 2014; Who, 2014).

It is essential to periodically calibrate all the equipment for measuring the temperature, in addition to the thermal qualification of the environments for their correct allocation (Taylor, 2001). The gathering of information that directly impacts on the thermal stability of the products, has become a requirement since March 2021, so that the set of actions that prevent the excursions are imposed until March 2022, according to article 89 of the CBR No. 430 (Brazil, 2020c).

In a survey of 1.175 pharmacies, 47.2% had refrigerators or refrigerators as preservation equipment, with exclusive use for thermolabile medicines and 7.8% had sharing with other products or foods. Only 41.3% of refrigerators had a thermometer to check the temperature (Costa et al., 2017; Leite et al., 2017).

For the conservation of products, the use of domestic refrigerators was prevalent. According to Taylor (2001), this equipment is only efficient for the storage of small volumes, even so, they reported that the domestic refrigerators do not have a precise control for the temperature control, being considered of high risk.

Lloyda et al (2014) confirmed that refrigerators have temperature excursions as a weak point. Part of this happens, therefore, this equipment was not designed for this use, it does not allow a sensitive temperature control, and is not recommended for this use (Taylor, 2001).

The Legislation in force through CBR No. 197 of 2017, requires the packaging of vaccines, in refrigerators registered with the National Health Surveillance Agency. These are classified as Class I, prohibiting the use of domestic refrigerators. However, conceptualizing vaccines as thermolabile drugs and aware that all thermolabile drugs must be packaged inside equipment that can ensure the ideal temperature of the products, the legislation pointed out is only specific for vaccines (Brazil, 2017n; Brazil, 2018a).

The refrigerators appointed by the National Health Surveillance Agency must be designed exclusively for the storage of pharmaceutical products, qualified and with the capacity for precision. This equipment must be exposed to all thermolabile drugs (Table 9). The absence of complaints in a scenario with a lack of tools to ensure product quality is at least unusual. Complaints are a tool that must be used to guarantee the quality of services and especially products. Complaints from customers is an indicator for quality analysis, as it highlights customer satisfaction with the service or product offered (De Almeida & Matias, 2016) Table 8).

Therefore, it should be considered as an indicator of process improvement, as non-conformities and deviations are scored through them. Each quality incident must be registered and classified as non-conformity or quality deviation, analyzed as valid and unfounded, investigated, punctuated the action plans, responsible and deadlines, and evaluated so that this incident is not recurring. If it is evidenced that this is a deviation from quality, contact the registration holder (Brasil, 2020c).

When non-compliance is related to thermolabile drugs that have undergone a temperature excursion, all affected drugs, lots and quantity should be described. Information regarding the excursion time and the exposure temperature are essential for decision making at the time of the investigation that must be conducted by pharmacists. The products must be sent to the quarantine area until the final decision, after consulting the product information (Ricote-Lobera et al., 2014).

It is worth noting that temperature excursions are cumulative, requiring stability studies to evaluate drugs after a chain break. Ricote-Lobera et al. (2014) also accentuate the possibility of laboratories making it difficult to send technical data sheets for products.

Every temperature excursion should be investigated to analyze whether the product remains safe to be administered. It is recommended that the recording of incidents be facilitated through the cold chain, not with the intention of stigmatizing it, but to guarantee the quality of the products, until the moment of administration to the patient.

It should be pointed out once again that the information on the stability study should not be used routinely, as the ideal conditions of conservation must be maintained throughout the cold chain, thus evidencing the quality of the products distributed. The absence of thermal mapping demonstrates that monitoring and thermal traceability may be carried out erroneously in approximately 58 out of every 100 establishments in the country. It is essential to inform that the purpose of thermal mapping is to highlight the critical points, whether positive or negative, in order to ensure adequate temperature monitoring. The thermal mapping must be carried out through three spatial plans and have a sufficient period to record all the cycles of workflows carried out (The United States pharmacopeial convention, 2012).

CBR No. 430/20 makes it clear that the allocation of equipment and instruments for monitoring temperature and humidity must be carried out according to the thermal qualification study, which will analyze the regularity and constancy of the temperature in relation to the time and space studied. This qualification must be redone whenever there is a significant change in the processes that may impact the quality of medicines (The United States pharmacopeial convention, 2012; Brazil, 2020c).

Regarding the qualification of passive thermal conditioning systems, the thermal qualification of the packages is intended to establish the period in which, within the configuration of the established conditioning materials, the medication is kept within the ideal temperature. The lack of knowledge of the thermal durability of the volumes makes it impossible to plan effectively when sending medicines, the points for exchanging thermal conditions during the routes, if necessary, and to know if the products transported are within the ideal temperature range. The thermal qualification of packaging has been discussed more intensively since 2017 when the National Health Surveillance Agency published the Transport Guide for biological products (Brasil, 2017c).

Therefore, ignorance of the thermal durability of the volumes is predominant for safe shipping via routes, or for the receipt of items through thermal packages, no matter how qualified they are. It is recommended that the volumes, on the outside, can highlight data such as the date and time of shipment, in addition to the thermal durability of each volume (Table 9).

The legislation aimed at Good Storage, Distribution and Transport Practices (GSDTP) has not been updated for at least two decades. In a brief analysis of the current legislation aimed at good storage and transportation practices, it lacks what concerns quality tools (Cardoso, 2015).

The main regulatory framework regarding GSDTP is definitely Ordinance 802, published and approved by the Ministry of Health. It can be seen that when this ordinance was drafted in 1998, the concern of regulatory bodies inspection was focused

on the identification of counterfeit products or fraudulent, punctuating product traceability and verifying original characteristics as extremely relevant activities, aiming to combat the consumption of adulterated, stolen and / or counterfeit products (Brazil, 1999).

Ordinance 802 establishes the Control and Inspection System, punctuating the structural aspects to ensure the quality of medicines, temperature control through periodically calibrated equipment, thermal mapping of the physical structure and reaffirming the obligation of the technician responsible registered with the class council pharmaceutical companies for distribution establishments (Brasil, 1999).

The ordinance describes the documentary structure for the wholesale activity, and the establishment must prepare and maintain the Good Practices´s Manual, the standard operating procedures for all processes that may impact on the quality of the products distributed and the propagation of these documents, which must be disseminated to everyone involved, as well as CBR No. 340 (Brazil, 1999; Brazil, 2020c).

The ordinance makes it mandatory to only operate with licensed carriers and imposes that the purchase of products must be made exclusively through manufacturers (BRAZIL, 1999).

The guideline regarding the acquisition of products only through record holders was one of the most controversial points of the current legislation, and it is necessary to understand the local health surveillance initially, to regulate the acquisition of products through wholesale companies, as long as these are licensed. and comply with Good Storage, Distribution and Transport Practices, until 2019, when through CBR No. 304, now replaced by CBR No. 430 of 2020, and after 21 years, there was an express regulatory directive of national scope, to transform purchasing between wholesale companies into a legal practice (Brazil, 1999; Brazil, 2019b; Brazil, 2020c).

The wholesale companies in front of this ordinance are placed as highlights for the population, for carrying out essential activities and impacting public health and safety, jointly absorbing the responsibility for the quality of the products (BRAZIL, 1999). For this, logistic companies must carry out their activities in order to maintain the conditions given by the manufacturers, including making the carriers used for the movement of products also follow these indications (Brazil, 1999).
Ordinance No. 802 is definitely the biggest regulatory framework, still partially in force in the country focused on the wholesale scope of products, today approved by the National Health Surveillance Agency. However, this is ineffective, as they do not require parameters to verify product quality in all logistical processes, so it is not possible to assess whether the products maintained quality after going through the logistics chain. This ordinance will be replaced in 2021, with the total implementation of CBR No. 430 (Brazil, 1999; Brazil, 2020c).

Aiming at greater population access to vaccines, the plateau decided to sanction vaccination activities in pharmacies and drugstores with the approval of Law 13.021 / 2014. However, even in force, the law could only be complied with the publication of CBR No. 197/2017 by National Health Surveillance Agency, which regulates the parameters for the operation of the vaccination activity in these establishments. One of the points of attention is the prohibition on the use of domestic refrigerators in the protection of vaccines, requiring the equipment used for conditioning to be regulated and registered by National Health Surveillance Agency (Brazil, 2014; Brazil, 2017n; Brazil, 2018a).

So far, no other legislation regulates the storage and handling conditions of the other thermolabile drugs, which are currently still being packaged in domestic refrigerators, equipment that is thermally unstable. Still in 2017, The National Health Surveillance Agency publishes the first reference for transporting products conditioned to a specific temperature, this being the Guide for the Qualification of Transport of Biological Products, only consultative documents, which points out the minimum conditions for carrying out the handling of products conditioned to a certain temperature. This document is not a legal guideline, often not being followed by the absence of the obligation (Brazil, 2017c).

The guide also points out that the type of transport chosen must be consistent with the product handled to ensure its quality on the most critical routes in terms of temperature, at any time of the year (Brazil, 2017c). The year 2017 was also the year in which The National Health Surveillance Agency began, through the publication of public consultation No. 343 on May 11, 2017, an attempt to update to replace Ordinance 802 19 years after its publication (Brazil, 1999; Brazil, 2017c; BRAZIL, 2020e).

The National Health Surveillance Agency uses public consultation with the aim of real popular participation, analyzing all contributions and publishing considerations at the end of the process. It is worth ratifying that public consultations are not intended to list a vote, the suggestions being analyzed one by one (Brazil, 2020e).

Participation in public consultations is vital, as it is only through contributions made by professionals in the area that are the subject of the change that the impact and the need for the changes can be assessed. Two years later, in September 2019, CBR No. 304 was published, but due to the lack of understanding on several points and the need for adjustments in March 2020, the "Questions and Answers" is published, clarifying doubts related to critical points the legislation and rectifying the deadlines for the implementation of the CBR (Brazil, 2019b; Brazil, 2020b; Brazil, 2020c).

However, this resolution is not widely accepted, especially by the handling / transportation companies, as it brings effective changes to guarantee the quality of products, punctuating the need for adaptation and qualification of vehicles to ensure the temperature of products within the specifications indicated by manufacturers, involving a high cost for this adaptation, due to the special conditions for the transport of thermolabile medicines (Brazil, 1999; Brazil, 2017e; Brazil, 2019b; Brazil, 2020b; Brazil, 2020c).

It is notable that the laws published today have a bias aimed at evidencing, tracking and ensuring the quality of products, punctuating actions for improvements, if necessary, during the processes performed, in opposition to Ordinance No. 802, published in 1998, when the view of Organs regulatory bodies aimed to ensure that counterfeit, adulterated and / or stolen products are not shown (Brazil, 1999; Brazil, 2017e; Brazil, 2019b; Brazil, 2020b; Brazil, 2020c).

Therefore, National Health Surveillance Agency, through the publication, in October 2020, of CBR No. 430, consolidates all the information on the modifications, and makes changes regarding the criteria for thermal monitoring of products, causing a loosening in the guidelines that previously imposed the obligation of qualification and thermal monitoring for all routes, removing all the items of article No. 84 of the CBR No. 304/19 (Brazil, 2019b; Brazil, 2020c).

CBR No. 430 brings with it greater importance in the set of actions that ensure the quality of products during the activities carried out by imposing greater control in these processes, titled as Good Storage, Distribution and Transportation Practices (GSDTP), and reaffirming joint and several liability of all involved (Brazil, 2020c).

Just like CBR No. 304, CBR No. 430 maintains immediately, art. 7, guaranteeing that the purchase of products, approved by National Health Surveillance Agency, by licensed distributors is legitimate, as long as they guarantee their traceability and the information is promptly recovered (Brazil, 2019b; Brazil, 2020c).

The administrative guidelines make it clear as to the responsibilities of each position or individual, which must have a process described through an organization chart and the training must be carried out individually and continuously for the performance and development of activities (Brazil, 2020c).

Training is mandatory for all employees who develop critical activities that directly impact the quality of products. The employees responsible for the Quality Management System (QMS) must have sufficient tools to carry out their activities and hierarchical autonomy under the audited, inspected and / or evaluated sectors (Brazil, 2020c).

Another concern is regarding the management of actions aimed at quality. For this, it is informed through the section "Quality Management System" that all processes that directly or indirectly intervene in the quality of products or services must be mapped and documented expressly through standard operating procedures (SOP). Non compliance with these Sops must be

seen as non-conformities (NC) and documented, investigated the root cause, and through grounded actions, develop processes for continuous improvement in procedures (Brazil, 2020c).

Good documentation practices (GDP) are punctuated in a pioneering way, making a SOP mandatory for the preparation of documents, the periodic review of documents, that this must be written in an understandable way and that they must be managed in order to be adapted to the reality of the documents.It also describes the correction of information, as long as it can be seen to attest credibility, and that documents must be retained for a minimum of 5 years (Brazil, 2020c).

Complaints are seen as a "thermometer" for processes, showing whether they are sufficient or need improvement. To this end, CBR No. 430 imposed the registration of all complaints, which must be judged to be well founded or unfounded, and in the case of those well founded, to be judged as deviation or non-conformities. The deviations must be directed to the industries, so that they take the necessary measures and non-conformities must be treated internally as already mentioned above (Brazil, 2020c).

Return processes must also be registered and handled internally. Before reintegrating products into the tradable stock, they must be evaluated by the pharmacist to ensure the quality of the reintegrated products, rejecting if the quality is doubtful (Brazil, 2020c).

CBR No. 430, unlike CBR No. 304 and its addenda, makes it clear that the reintegration of recovered products from theft, theft or misappropriation, may return to the marketable stock, if the QMS can conclude that the products are adequate in terms of quality and guarantee their effectiveness and safety (Brazil, 2019b; Brazil, 2020a; Brazil, 2020b; Brazil, 2020c; Brazil, 2020c).

Self-inspection programs must be implemented in companies with a justified period and with a frequency capable of ensuring that all activities that interfere with the quality of products can be evaluated. This will be carried out by qualified employees who do not have direct involvement in the inspected activity (Brazil, 2020c).

Temperature monitoring is enforced through various guidelines throughout the new DRC. This reinforces Ordinance No. 820/98 in which the gauging equipment must be periodically calibrated and positioned according to the environmental qualification study, verifying the critical points of the products' storage structure. The measurements must also be recorded, which should occur automatically, according to good practices, automatically. Records must be archived for a period of 2 years (Brazil, 1999; Brazil, 2020c).

CBR No. 304 would bring about an effective change regarding the monitoring of routes, however CBR No. 430 removes the provisions of Art. 84 and makes thermal monitoring of vehicles unnecessary for the movement of products, whose routes are less than one period of 8 (eight) hours and have as their final destination the dispensing of medications to patients, therefore, essential information to guarantee the thermal stability of the medications is lost caused by the removal of these guidelines, and the logistical chain, mainly focused on thermolabile products , be potentially harmful due to the loss of product effectiveness, resulting in therapeutic inefficiency, and the formation of toxic products due to the instability of pharmaceutical products (Brazil, 2019b; Brazil, 2020c).

The transport of thermally labile products must be done through passive or active solutions, previously qualified and the conditioning materials of passive packaging can be replaced by outsourced transport companies, provided that they have prior authorization and that the professionals involved are trained for this procedure, following the guidelines for the qualification of the packaging previously made (Brazil, 2020c) (Table 10).

5. Conclusion

Aware of the criticality in transportation and planning for cargo handling, continuous thermal traceability is the most effective tool to ensure the quality of thermolabile drugs. It was possible to show that the cold chain today is potentially dangerous for the maintenance of the quality of thermolabile medicines, being able to reach the final consumer altered and cause damage to the patient, either through the formation of toxic products, or due to therapeutic inefficiency.

It was seen that pharmacists take an average of 3 years after graduation to seek training. And, most of them, postgraduates at the level of specialization, are not trained to deal with thermolabile drugs, as they do not have specific training on the topic, and they still had a deficiency in the issues raised related to these products. Topics such as stability, notions of legislation, the cold chain, qualification and validation processes for equipment and environments, and product knowledge, should be discussed thoroughly, to make the professional familiar with these contents and supporting their routines.

The difficulty in accessing the technical data sheets of the products hinders a factual analysis for dealing with incidents and the implantation of process improvement processes. When raising an overview of the conditions of storage, distribution and transport, several proved to be inadequate.

Failures in the control, monitoring and thermal traceability of the cold chain are potential causes of quality incidents that led to the disposal of many drugs evidenced in this work, impacting economically on the processes, in addition to possible damage to patients. Non-conformities could still be seen in the use of refrigerators, such as the storage of food and beverages next to medications and incorrect storage at doors or close to the freezer.

These could easily be resolved through training and routine monitoring. It was possible to verify the existence of tools. However, they are either not used, or the tools used are unsuitable for monitoring and conserving products, such as thermometers for measuring and domestic refrigerators for the conservation of products. Through several studies, it was found that periodic manual monitoring is ineffective due to flaws in the records and the inefficiency in capturing temperature excursions.

In addition to this problem, the lack of thermal mapping and the lack of knowledge about the thermal durability of the packaging corroborate the inefficiency of the national cold chain of medicines. When informing that the medications are not analyzed after going through an excursion process, the responsible ones endanger the health of the patients, in which the medication will be administered.

Tools for continuous thermal monitoring in real time that can issue reports of thermal traceability and taking action in the event of any incident, are the most indicated, in addition to having alarms that allow the immediate intervention of the professionals involved in the case of temperature excursions.The absence of thermal traceability and professional training makes one of the main control tools that are the complaint useless, which proved to be non-existent.

Turning to the analysis of the deontological guidelines, it was possible to show decades without any significant update. This lack of updating can be potentially harmful, as companies usually follow minimally the legal guidelines to establish their internal processes and thus comply with what is required.

It is popular knowledge, the requirement of some aspects based on the Good Practices of Distribution, Warehousing and Transport, however these requirements lead to an absence of standardization, taking as usual, the specific knowledge of each municipal or state regulatory body, causing in a lack of general understanding of what is actually required.

In view of this, it is necessary to publish new guidelines that allow a greater diffusion of ideas, in addition to the availability of lectures, training and capacitation of the local inspection bodies, based on the parameters established by the National Health Surveillance Agency.

It is also necessary to periodically review the regulations, so that it can keep up with technological, administrative and logistical developments, resulting in publications of legal guidelines that impose continuous improvements in the processes and the continuing education of the professionals involved. It is hoped that the total implementation of CBR No. 430 in March 2022, may bring some tools that show and ensure the performance of the processes administered by the Quality Assurance and Control Management System, and thus ensure the quality of finished products until its administration by the patients.

It is highly advised that information such as the thermal durability of the packaging, the date and time of arrival, and all other information that has an effect on the thermal stability of the products and helps to ensure it is made clear externally so that the expert concerned can determine the receipt of the products.

The availability of the technical data sheets of the products and the training of professionals in the entire logistical chain by the holder of the registration must come clearly in a rectification of CBR 301/2019 or, in the future, Questions & Answers related to this, with the intention to guarantee the quality of the product during all the process. CBR No. 197/2017, already published by National Health Surveillance Agency and fully in force, should be expanded in the conditioning equipment requirement, in order to guarantee the quality of all thermolabile medicines, and not just vaccines, making household refrigerators unusable.

There is potential guidance on improving drug formulations to make them more and more stable at room temperature. New technologies are already available in order to ensure the control and monitoring of the temperature of thermolabile drugs during their storage and movement. Some laboratories, to monitor the quality of the products distributed, forward the cargo together, irreversible temperature monitors, which in case of excursions, show a message, and the distributor must return the entire cargo.

The limitation of this tool is that it does not reach the entire chain, generally reaching only wholesale establishments. The use of active systems, through thermal boxes with batteries or the like, or passive systems through qualified thermal packaging, can guarantee the temperature in ideal conditions and are already a reality.

As well as coupled thermal monitoring systems, continuous electronic monitoring systems, among other equipment, can guarantee thermal temperature monitoring through the issuance of reports. Some of these even allow real-time monitoring of the load, so that in the event of a temperature excursion, immediate actions can be taken.

The performance of pharmacists is crucial in recording and dealing with quality incidents, directing not only corrective, but also preventive actions, acting in the continuous improvement of the process, which is required by current legislation. The training of the professionals involved is even more necessary at this time, as CBR No. 430, will require professionals to adopt a posture focused on Quality Assurance Management, mainly related to thermolabile products.

Based on this problem raised and answered through this systematic evaluation of the cold chain, a study is expected to evaluate thermolabile drugs at various points in the logistical processes, to determine the products in a randomized manner, in order to verify stability, to make reduction principle active, the formation of toxic products arising from thermal discipline and the validation of the product's expiration date.

Funding

This work was supported by Coordination for the Improvement of Higher Education Personnel (CAPES) through the Social Demand Program (DS) 88882.461736/2019-01.

Acknowledgements

Authors are thankful to the Regional Councils of Pharmacies from all over Brazil who contributed directly and indirectly to the research, the Federal Council of Pharmacy in Brazil, the Coordination for the Improvement of Higher Education Personnel and the Postgraduate Program in Pharmaceutical Sciences at the Federal University of Pernambuco for his kind support.

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