TECHNICAL REPORT

Workshop on Good Distribution, Storage and Transport Practices of Drug Products

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CONTEXT

There is a growing concern about the proper storage and transportation of finished drug products, because storing and transporting products outside their storage specification can potentially impact product stability, quality, efficacy, and safety.

In an attempt to regulate the pharmaceutical supply chain, certain national health legislation and international regulations have been enacted and updated in recent years. In Brazil, due to concerns brought forward by various pharmaceutical supply chain stakeholders, the National Health Surveillance Agency (ANVISA) published the Public Consultation No. 1,077, on February 23, 2022, with the objective of revising the initial text.

The objective of the Public Consultation No. 1,077, as stated by ANVISA, is to update the Resolution of the Collegiate Board of Directors - RDC No. 430/2020 with a view towards the implementation of a risk-based approach to managing the storage and transportation of drug products, similar to what has been outlined by other international regulatory agencies and the United States Pharmacopeia (USP). It was the intention of ANVISA to determine a feasible deadline for understanding the various transportation routes (considering that Brazil is a continental country), execute a risk analysis, and implement, control and/or monitor medicines during transport in Brazil (ANVISA, 2022).

In March of 2022, the USP, SINDUSFARMA (Brazilian Pharmaceuticals Industry Union), and the Brazilian National Academy of Pharmaceutical Sciences (ACFB/ANF) held a workshop on Good Storage and Transport Practices. The event was attended by more than 800 participants (including ANVISA, Trade Associations, manufacturers and academia) with the following being presented: regulatory framework for the storage and transport of drug products in Brazil, updates on risks and risk mitigation strategies for drug storage and transport processes, and the use of Mean Kinetic Temperature (MKT) to evaluate excursions. In addition, two Brazilian studies were presented which looked at lane mapping and the use of MKT in Brazil.

The workshop had two sessions with six presentations (see Table 01). The first session was moderated by Luciana S. Takara, Associate Governmental and Regulatory Affairs Director at USP, and it gave an overview of the storage and transport of medicines and current trends. The session had three presentations, two presented by USP Packaging and Distribution Expert Committee members and one by a USP Senior Principal Scientist.

The second session was moderated by Rosana Mastellaro, SINDUSFARMA's Technical Regulatory and Innovation Director, and gave an overview of the storage and transport of medicines in Brazil with speakers from ANVISA and representatives appointed by the pharmaceutical associations.

Access the slides and recordings of the workshop here.

Table 1. Summary of the lectures of workshop on Good Distribution, Storage and Transport Practices of Drug Products.

First session **Storage and Transport of Medicines: Overview and Trends** Moderator: Luciana S. Takara – USP	
Lecture 1 – USP's Efforts in Distribution: History and the new USP General Chapter <1079>. General Chapter Family & What's Next?	Dr. Desmond Hunt, USP
Lecture 2 - USP General Chapter <1079>: Risks and mitigation strategies for the storage and transport of medicines	Dr. Glaucia Karime Braga, Qualitaspharma
Lecture 3 - USP General Chapter <1079.2>: Mean Kinetic Temperature (MKT) in the evaluation of temperature excursions during drug storage and transport	Chris J Anderson, Cardinal Health
Second session **Good Distribution, Storage and Transport Practices of Medicines in Brazil** Moderator: Rosana Mastellaro – SINDUSFARMA	
Lecture 4 - Regulatory Framework on Good Practices for Distribution, Storage and Transport of Medicines - RDC 430/2020 and future perspectives	Felipe Augusto Gomes Sales, GIMED/ANVISA
Lecture 5 - Mean Kinetic Temperature in different regions of Brazil	Dr. Lauro Moretto, ACFB/ANF Dr. Nelson Rafael Matta Vals
Lecture 6 - Brazilian study on lane temperature mapping	Eliéte Carrara, ITA Fria Dr. Nelson Rafael Matta Vals

Below is a summary of each presentation, where important concepts and best practices for the storage and transport of medicines have been highlighted.

Disclaimer: *The organizing authors of this technical report structured the information shared at the event. The responsibility for the content accuracy and bibliographic citations used in the lectures is exclusive to each speaker.*

Lecture 1 - USP Efforts in Distribution: History and the new USP <1079> family of general chapters & What's Next?

Speaker: *Dr. Desmond G. Hunt, USP – Senior Principal Scientist*

The presentation addressed the following points:

- How and why USP became involved in the topic of storage and distribution of drug products
- Activities carried out by USP in the past that support the organization's current positions
- General chapters developed by USP and plans for developing future chapters around the topic of drug storage and transport.

According to the speaker, the USP started discussing drug storage and distribution activities during the 1995 USP Convention. At this time, concerns were raised about the distribution of temperature sensitive medicines outside their storage specification. Thus, Resolution 10 was adopted, which encouraged USP to identify drug products for which storage and transport were of special concern (temperature sensitive). Resolution 10 also

mandated that work be done to include information on the proper storage in USP drug product monographs, to ensure that product integrity is maintained throughout the supply chain.

Studies conducted between 1997 to 2000 sought to better understand temperature variation during storage and transportation and how this could impact drug product stability. In addition, these studies aimed to understand how to avoid such temperature excursions leading to the development of USP General Chapter <1079> Good Storage and Distribution Practice, which became official in 2004.

In 2012, USP held a USP Supply Chain workshop and, post-event, developed comprehensive guidance on the proper storage and distribution for all compendial articles (active ingredients, excipients, drug products, and dietary supplements), <1083> on Good Distribution Practices. During this period, USP developed recommendations on good drug import and export practices, as well as on how to ensure the safety and integrity of products as they move through the pharmaceutical supply chain.

However, due to the Drug Quality and Security Act (DQSA), which was enacted by the US Congress in November 2013, USP decided not to move forward with making this chapter due to potential conflict and overlap with the US Food and Drug Administration (FDA) guidance that was planned for development in response to the enactment of the new law.

This redirected USP's effort towards revising <1079>, a chapter that only provided general guidelines, to one that incorporated a risk-based approach to the storage and transport of finished drugs, as well as mitigating strategies to help minimize certain risks.

The revision of <1079> was the starting point for USP to build a family of general chapters meant to address various aspects related to drug product distribution. Table 2. below shows the <1079> family of chapters and their status.

Table 2. Family of <1079> chapters and their status.

Family of General Chapters <1079>		
Current	**Published in the Pharmacopeial Forum for public consultation**	**Under development**
<1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products	<1079.3> Monitoring Devices – Time, Temperature and Humidity PF 48 (4) July, 2022	<1079.5> Qualification of Shipping Systems
<1079.1> Storage and Transportation of Investigational Drug Products	<1079.4> Qualification of Storage Areas (Temperature Mapping) PF 48 (5) September, 2022	<1079.6> Transport Route Profiling Qualification
<1079.2> Mean Kinetic Temperature in the Evaluation of Temperature Excursions during Storage and Transportation of Drug Products		<1079.7> Information Systems for Distribution – Validation/Verification Studies

The Dr. Hunt closed his talk by inviting stakeholders to participate in the public consultation processes of USP general chapters, published in the Pharmacopeial Forum, as well as sending questions via e-mail dgh@usp.org.

Lecture 2 - USP General Chapter <1079>: Risks and mitigation strategies for the storage and transport of medicines

Speaker: *Dra. Glaucia Karime Braga – Qualitaspharma and Member of the USP Expert Committee on Distribution and Packaging and Co-Chair of the USP General Chapter Subcommittee <1079>*

The presentation addressed the following points:

- Holistic view of the pharmaceutical supply chain
- Rationale used in the development/revision of <1079>
- How product and process knowledge are starting points for risk identification
- How risk mitigation categories are elements of a Quality Management System

The speaker discussed a holistic view of the pharmaceutical supply chain by highlighting the following factors:

- The complexity of the supply chain with multiple supply chain partners (i.e., different entities that are part of this chain)
- Two key activities common to all supply chain partners: storage and transport
- The use of different modes of transport allows the movement of product along the supply chain, from manufacturer to customer
- Global supply chains can have different local regulations and different climatic zones serving as complicating factors
- All supply chain partners have joint responsibility

Chapter <1079> is a comprehensive chapter and presents USP current thinking on drug storage and transportation. In the development of this chapter, USP used ICH Q9 (Quality Risk Management) as a guideline, specifically the steps for identifying and reducing risks. The essence of <1079> is presented in Figure 1, which shows that product and process knowledge are the starting points for risk identification.

Product knowledge includes, but is not limited to the following:

- Intended use
- Storage conditions
- Potential hazards to the environment and personnel (e.g., hormones, cytotoxic drugs, and radiopharmaceuticals)
- Inherent vulnerability (e.g., high potential for abuse, high value drugs, attractiveness of cargo theft, counterfeiting, and diversion)

Process knowledge includes, but is not limited to, the following:

- Knowledge of supply chain partners
- Transport modes (air, sea, rail, road, or a combination of modes)
- Transport routes
- National and international regulations

Understanding these factors helps the organization/company to identify their associated risks. Process mapping is a useful tool for understanding a particular process

and/or operation (e.g., transport lane selection or loading/unloading patterns of warehouses and vehicles).

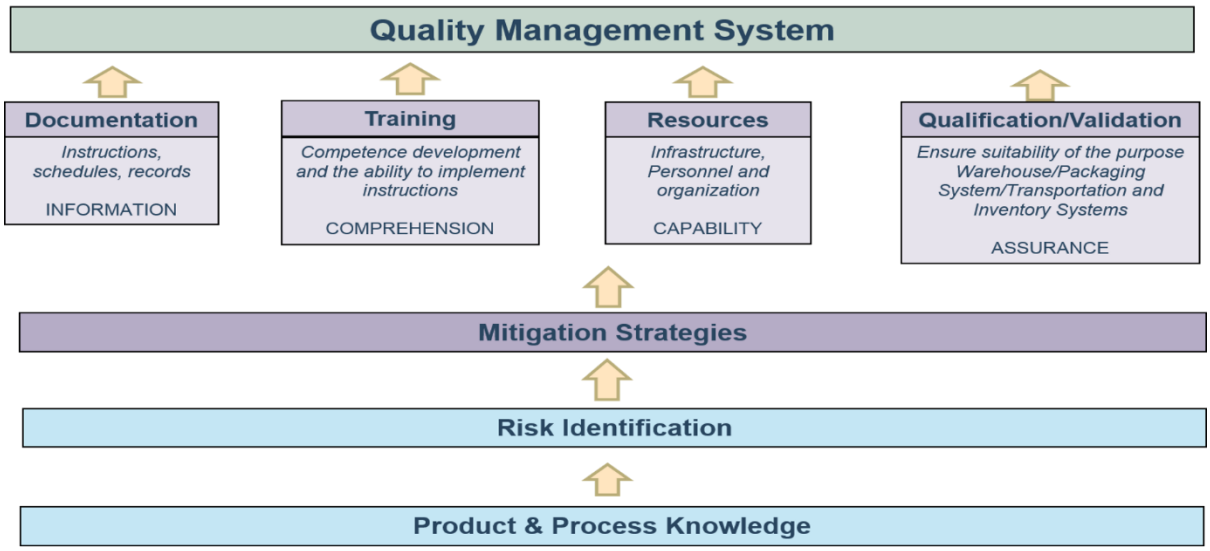
The risk identification is the systematic use of information to identify potential sources of harm (hazards). Information may include historical data, theoretical analysis, informed opinions, knowledge of products and processes, and stakeholder concerns. Risk identification addresses the question, "What can go wrong?". Mitigation strategies are part of the risk control process, specifically risk reduction. Risk reduction addresses the question, "What can be done to reduce or eliminate risk?". Thus, risk mitigation may include actions taken to mitigate severity, decrease the likelihood of occurrence, or increase detectability.

Once the risks have been identified, it is possible to establish risk mitigation strategies. Such strategies, when implemented, will provide the organization/company with the autonomy to plan, implement, measure, and improve its processes, in accordance with current regulations and associated risks. Generally, mitigation strategies fall into one of the following four categories:

- Documentation (i.e., providing instructions for a specific operation or process to standardize it and establish consistency)
- Training (i.e., assurance of competence)
- Resources (i.e., providing infrastructure and human resources)
- Qualification and validation (i.e., ensuring that resources and processes are reliable, reproducible, and robust)

And these four risk mitigation categories are elements of a Quality Management System.

Figure 1. Risk-based approach to a Quality Management System. Source: USP GC <1079>.



Different stakeholders perceive risks differently. But regardless of where the organization fits in the supply chain, consideration of risks and the mitigation actions taken must reflect the potential impact across the supply chain. According to the speaker: "when looking at the Supply Chain with this risk-based approach, it is possible to communicate risks and disseminate knowledge among these partners in a better way, and this goes beyond fulfilling requirements of a regulation; this empowers the supply chain partners in their decision-making process".

To close the presentation, the speaker highlighted that "<1079> provides an important tool for organizations to use as a guide to develop their processes and have a quality management system based on risk".

See <1079> *Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products* to find some risks and mitigation strategies for these risks for all processes related to the storage and transport of medicines, in addition to a table containing the applicability of each mitigation strategy for each entity in the supply chain.

Lecture 3 - USP General Chapter <1079.2> Mean Kinetic Temperature (MKT) in the evaluation of temperature excursions during drug storage and transport

Speaker: *Chris Anderson – Cardinal Health and Member of the USP Expert Committee on Distribution and Packaging and Co-Chair of the USP General Chapter Subcommittee <1079>*

The presentation addressed the following points:

- The use of MKT to evaluate temperature excursions
- Definitions and excursion limits for *Controlled Room Temperature* (20° C to 25° C) and *Controlled Cold Temperature* (2° C to 8° C)
- Examples of proper and improper use of MKT for the handling of temperature excursions.

The speaker highlighted that, although every effort should be made to store and distribute drug products within the temperature range indicated on the packaging, temperature excursions can occur. The use of Mean Kinetic Temperature (MKT) in evaluating excursions, as recommended by <1079.2> *Mean Kinetic Temperature (MKT) in the Evaluation of Temperature Excursions During Drug Storage and Transport*, will allow for responsible temperature excursion management.

Therefore, it is necessary to answer the following questions: What is the concept of MKT? What are the allowed excursion limits?

MKT is defined as the single calculated temperature at which the total amount of degradation during a given period is equal to the sum of the individual degradations that would occur at various temperatures. It is a way of summarizing the exposure time history of a product with a single "effective" or "virtual" temperature. Thus, MKT integrates the time-temperature history by making assumptions about the kinetics of chemical degradation of a product.

USP recommends the use of MKT for handling excursions whose limits are set forth in <1079.2> and <659> *Packaging and Storage Requirements* for products stored at Controlled Room Temperature (20° C to 25° C) and Controlled Cold Temperature (2° C to 8° C), as shown in Table 3.

Table 3. Allowable excursion limits for *Controlled Room Temperature* (CRT) and *Controlled Cold Temperature* (CCT) established in General Chapter <659>.

	CRT – *Controlled Room Temperature*	**CCT – *Controlled Cold Temperature***
Temperature range for storage (label)	20° C to 25° C	2° C to 8° C
Mean Kinetic Temperature (MKT)	NMT* 25° C	NMT 8° C
Time period for calculating the MKT	30 days**	24 hours
Acceptable excursion range	15° C to 30° C	2° C to 15° C
Maximum temperature	NMT 40° C	Not less than 2° C and not more than 15° C
Maximum excursion time	24 hours	24 hours

*NMT: acronym for *Not More Than*
** 30 days or the average number of days a product remains in the organization's possession

Regarding the MKT calculation, the speaker mentioned that there is validated software that can be used for calculating MKT and highlights that "MKT is different from an arithmetic mean, with MKT generally being higher". In addition, he also points out that "to calculate MKT for CRT, USP recommends using the highest and lowest temperature for each day (although all available data can be used, as it increases the accuracy of your calculation); for CCT, USP recommends using all temperature points recorded over a given time frame". During the workshop, examples on how to use MKT were presented. However, to help workshop participants better understand the proper and improper use of MKT two important references on the topic where supplied:

- Anderson C, Seevers R, Hunt D. The Use of Mean Kinetic Temperature to Aid Evaluation of Temperature Excursions for Controlled Cold Temperature Drugs: Proper and Improper Application. *Pharm. Forum* 2019;45(5)
- Anderson C, Seevers R, Hunt D. The Use of Mean Kinetic Temperature to Aid Evaluation of Temperature Excursions: Proper and Improper Application. *Pharm Forum*. 2018; 44(4)

Another important point highlighted by the speaker is about frozen products: "For frozen products, such as frozen COVID-19 vaccines (-20° C and -70° C), USP does not currently recommend an excursion range outside of what has been published by manufacturers. Furthermore, USP currently does not recommend using MKT to evaluate any COVID-19 vaccine excursions or any other frozen, ultra-frozen, or cryogenic product excursion."

To conclude, the speaker warned: "Do not abuse MKT," as it is a tool that can be used to evaluate temperature excursions in specific situations. MKT cannot be used to normalize situations that are out of control. Thus, the use of MKT in evaluating a short-term excursion (as defined in <659> and <1079.2>) and the timeframe used to calculate MKT as recommended by USP, will allow for responsible management of excursions."

Lecture 4 – Regulatory framework on Good Distribution, Storage and Transport Practices of Medicines, Brazilian Resolution - RDC No. 430/2020 and future perspectives

Speaker: *Felipe Augusto Gomes Sales, ANVISA*

The presentation addressed the following points:

- The context in which Resolution of the Collegiate Board of Directors - RDC No. 430/2020 was published
- The results of Public Consultation No. 1,077/2022
- The changes incorporated into RDC No. 430/2020

The ANVISA speaker informed that Brazil was behind schedule and needed to align itself with international practices regarding the distribution of drug products. In this context, Resolution of the Collegiate Board of Directors - RDC Nº 430/2020 was published (provides for Good Distribution, Storage and Transport Practices of Medicines), and has text very similar to PIC/S (Pharmaceutical Inspection Cooperation Scheme).

However, many stakeholders, especially the associations representing the pharmaceutical supply chain, asked ANVISA to adjust the regulation because of the potential impacts of its implementation. Thus, ANVISA published the public consultation No. 1,077/2022, to propose an amendment to RDC No. 430/2020. The results of the public consultation were presented at the workshop.

It is noteworthy that the topic was evaluated and deliberated by the Collegiate Board of ANVISA on the same day as workshop, resulting in the publication of RDC No. 653/2022, which amended RDC No. 430/2022. According to the speaker, the regulation underwent 02 (two) punctual adjustments. The first refers to the amendment of art. 64 of RDC No. 430/2020, with the insertion of a provision on risk analysis. The second is the extension of the deadlines set out in art. 89, which will give more time to implement the regulations, especially by transporters.

Regarding risk assessment and decision-making based on facts, the speaker stressed its importance, but also recognized that time is needed for adjustments, which would justify the changes: “Risk analysis is fundamental and is a cultural issue. It is not overnight that Brazilian logistics will internalize (...) what a risk analysis is, how to do it, how to assimilate it, how to take it to the logistics segment in a more feasible way”.

In addition, the speaker also stated that: “the main gain of this update is to be able to use technical, reliable information that provides support for decision making, whether in the choice of transport suppliers, or in the choice and application of specific solutions for products with specific features.”

Finally, regarding the understanding of the use of the MKT, the speaker stated that: “No Brazilian regulation can obstruct a technological evolution. If there are technological developments, studies, scientific basis, all this can and should be applied, as long as it is used in a complementary way. Not as an absolute replacement, as a study done in one setting cannot be mirrored in a different setting.” Thus, MKT can be understood as a quality tool.

Lecture 5 – Mean Kinetic Temperature in different regions of Brazil

Speakers: *Dr. Lauro Moreto – Brazilian Academy of Pharmaceutical Sciences of Brazil (ACFB/ANF), President Emeritus & Dr. Nelson R. Matta Vals*

The presentation addressed the following points:

- Background on stability studies and origins of MKT
- The methodology and results of the study on "Mean Kinetic Temperature in different regions of Brazil" conducted by the speakers

The speakers presented a brief history of stability studies and the application of virtual temperature and MKT (Table 4), using data obtained from different methodologies from different cities and geographical regions within Brazil (Table 5).

Table 4. Summary of stability studies and MKT concepts.

Before 1967	• There were no regulations for drug stability studies • Companies carried out stability studies with their own criteria
1967	• Appeal from health authorities to the Director of the World Health Organization (WHO) to set up a working group to prepare recommendations and define international criteria for stability studies of drugs
1969	• OMS Publication – TRS 418 – *Draft Requirements for Good Manufacturing Practices in the Manufacture and Quality Control of Drugs and Pharmaceutical Specialties* - WHO Expert Committee on Specifications for Pharmaceutical Preparations, Twenty-second Report, Technical Report Series No, 418, Geneve, 1969.
1971	• Haynes, J.D. (1971) publication – *Worldwide Virtual Temperatures for Product Stability Testing*. J. Pharm. Sci., 60(6): 927-929, 1971. The following points of the study were highlighted: ✓ Questions how stability studies could be carried out based on the climatic conditions existing in different countries ✓ Proposes to use the modified Arrhenius formula to evaluate the degradation of chemical substances in relation to temperature ✓ Correlates the rate of degradation with the temperature and relative humidity of the air ✓ Establishes criteria and calculates the Virtual Temperature of 15 cities in the USA and 15 cities in other countries, including Brazil (Rio de Janeiro, Porto Alegre and Salvador)
1985	• Grimm, W. (1985) publication – *Storage Conditions for Stability Testing – Long Term Tests*. Drugs Made in Germany, 28/29: 1-12, 1985/1986. The following points of the study were highlighted ✓ Mean Kinetic Temperature Concept: the same as Virtual Temperature ✓ The MKT was calculated by taking the mean of the average annual temperatures, obtained at 7 am and 2 pm of each day, in each month. ✓ The average MKT values of the cities of each Climate Zone were gathered in a table with a proposal of standardization of stability studies. • WHO used data from studies by Haynes, J. (1967) and Grimm, W. (1985) to establish climatic zones, storage conditions and propose a global model for the study of drug stability.

2007	• Bott, R. F., Oliveira, W.P. (2007) publication - *Storage Conditions for Stability Testing of Pharmaceuticals in Hot and Humid Regions*. Drug Dev. Ind. Pharm., 33:393–401, 2007. ✓ The study presented MKT calculation of the 5 geographic regions and the average of Brazil, relating the number of days with temperatures >30° C. Bott & Oliveira – Mean Kinetic Temperature – MKT of Brazil (Please include reference

Source: Content extracted from the slides of the lecture "Mean Kinetic Temperature in different regions of Brazil", authored by Dr. Lauro D. Moreto and Dr. Nelson R. Matta Vals.

Afterwards, the speakers presented the preliminary results of their study on MKT, highlighting that it is "preliminary work of a prospective and interpretative nature, with its own concepts and methodology, prepared for comparative purposes with data available in national and international publications, and which, therefore, does not present final and conclusive results, nor does it constitute the position of entities or companies to which the authors develop or have developed activities".

The study methodology consisted of collecting data from INMET Automatic Stations (Brazilian National Institute of Meteorology) for 12 months in 2020. Measurements were carried out in the 27 capitals and in Brasília/DF. In cases where data was not available, temperature data was collected from other cities in the same state. The Average Temperatures (TM) (daily, monthly, and annual), MKT, and curves of variation of daily temperatures (24 h) (monthly and annual averages) were calculated. The study demonstrated that the MKT of the 5 regions of Brazil present lower values than those obtained by Bott & Oliveira (2007), as shown in the table below:

Table 5. MKT in the 05 Regions of Brazil (Bott & Oliveira; 2007 and results presented by Dr. Nelson Vals & Dr. Lauro Moretto).

Region (Brazil	Bott & Oliveira – MKT - ° C	Vals & Moretto MKT - ° C
North region	28,07	27,7
Northeast Region	28,23	27,4
Midwest region	26,24	25,5
Southeast region	24,21	22,8
South	22,51	24,1
Average in Brazil	27,12	25,9

In conclusion, the speakers commented that:

- The methodologies for calculating MKT for the cities and regions in Brazil were established with subjective criteria
- There are provisions established based on MKT data, contained in an ICH and WHO document, which present asymmetries in relation to the regulations of climate zone IV countries
- It is necessary for an accredited body to calculate MKT for Brazil and its geographic regions
- Official MKT values should be used to support the regulation of pharmaceutical activities related to the storage, distribution, and commercialization of health products in Brazil.

Lecture 6 – Brazilian study on lane temperature mapping

Speakers: *Eliéte Carrara, Ita Fria & Dr. Nelson R. Matta Vals*

The presentation addressed the following points:

- Rationale for the selection of routes to be mapped
- The methodology and results of the study on "Brazilian study on route temperature mapping"

The speakers presented a Brazilian study on lane mapping, which was developed at the request of the Brazilian Association of Pharmaceutical Wholesale (ABAFARMA) and the Brazilian Association of Distribution and Logistics of Pharmaceutical Products (ABRADILAN). The first stage of the study consisted of selecting the routes to be mapped. For this, a survey was made of the historical temperatures (in 2018 and 2019) in the cities where the distribution centers of the aforementioned associations are based. The cities with the highest temperatures were selected, resulting in 20 cities be selected from the 5 regions of Brazil.

Based on a risk analysis, lanes where selected. The following factors were considered in selecting the lanes: (i) distance between the original Distribution Center and the last delivery; (ii) delivery time; and (iii) temperature of the city of the last delivery. In locations or distribution centers with similar characteristics, the lane with the greatest distance was selected. Thus, 20 lanes were selected.

The temperature mapping was carried out in January, February, March, April, May, July, November, and December 2020. As explained by speakers, these were the months with the highest historical temperatures. During the presentation, an official letter from ANVISA was quoted (number and date of this letter was not informed) which states that the Agency accepted temperature mapping studies in months with higher temperatures, when these records occurred outside the summer season.

As for the contents of the study package, four 10 mL saline flasks packed in a cardboard or kraft paper shipping box were used. The internal temperature (data-logger attached to the product) and external temperature of packages (data-logger attached to the external side of the package) were monitored. The load for each route contained 6 packages per vehicle and therefore 12 temperature loggers per vehicle. The lane mapping study was performed in triplicate.

Brazilian legislation establishes 30°C as the upper temperature limit for storage and transport of medicines, as the country is located in climatic zone IVb. This criterion characterizes temperature excursion values above 30°C without taking into account the MKT concepts, even for products that were challenged in stability studies in isotherms of 30°C and 40°C.

The authors concluded that "the monitoring of the temperature of critical routes foreseen in the RDC N. 430/2020 is feasible and where the temperature was higher than 30°C could demand a solution supported by stability studies and MKT calculations. Finally, they also demonstrated that the temperature fluctuations recorded on 19 routes are compatible with the ICH and WHO MKT concepts, making it necessary to establish coherent limits for climate zone IVb".

Table 6. Lanes Mapped in the Brazilian Study

Route	Origin	Destiny	MKT °C	Journey time	Recording time above 30° C	Registration above 40° C
1	North RO Region	Nova Brasilândia do Oeste/RO	27.5 °C	5.75 h	0 h	No
2	RJ Metropolitan Region	Itaoacara/RJ	22.3 °C	5.75 h	0 h	No
3	Metropolitan Region Vitória/ES	Belford Roxo/RJ	26.3 °C	20.75 h	0 h	No
4	Metropolitan Region Porto Alegre/RS	Itaqui/RS	24.8 °C	3 h	0 h	No
5	Countryside of the Stateof SP	Brasilia DF	25.5 °C	8.25 h	0 h	No
6	Northeast Region AM	Eirunepé/AM	27.7 °C	440 h	110 h	No
7	Midwest Region MS	Porto Murtinho/MS	22.3 °C	12.75 h	1h	No
8	Metropolitan Region Recife/PE	Petrolina/PE	29 °C	8.50 h	3.75 h	No
9	Metropolitan Region BH/MG	Uberlândia/MG	25.8 °C	21.75 h	1 h	No
10	Southern Region SC	Itapiranga/SC	24.3 °C	8.50 h	2 h	No
11	Metropolitan Region Natal/RN	Lucrecia/RN	28.1 °C	10.50 h	2.25 h	No
12	Metropolitan Region Goiânia/GO	Jataí/GO	25.6 °C	24.25 h	0.25 h	No
13	Central-South Region MT	Vila Rica/MT	27 °C	70, 50 h	5.50 h	No
14	Palmas/TO Metropolitan Region	Axixá do Tocantins/TO	28.5 °C	40 h	8.50 h	No
15	Teresina/PI Metropolitan Region	Parnain/PI	29.4 °C	9.25 h	2.75 h	No
16	Countryside State of SP	Santa Fe do Sul/SP	27.9 °C	7.25 h	6 h	No
17	Metropolitan Region João Pessoa/PB	Cajazeiras/PB	29.9 °C	25.75 h	9 h	No
18	Metropolitan Region Rio Branco/AC	Cruzeiro do Sul/AC	29 °C	111 h	24.50 h	No
19	East Region BA	Barrier/BA	28.7 °C	9.50 h	4.50 h	No
20	Metropolitan Region Aracaju/SE	San Francisco/SE	30.4 °C	6 h	7.25 h	Yes

Source: Data were extracted from the presentation of the Brazilian study on lane mapping. The city of origin was not presented so that it is not possible to identify the company whose route was monitored. The frame formatting was prepared by the authors of this report.

Finally, the speakers highlighted the need to broaden the discussion on MKT and on the need to unite all links in the pharmaceutical chain: "sharing studies, disseminating knowledge, participating in discussions is essential to have the segment strengthened".

Final considerations

The workshop brought together experts who presented updates related to the distribution of medicines, such as: the Brazilian regulatory framework on the topic, identification of risks and risk mitigation strategies in storage and transport processes, use of MKT in lane mapping and treatment of temperature excursions.

The MKT can be used as another quality tool, when combined with lane mapping and a robust risk analysis (including products and distribution processes), for evaluating temperature excursions and for temperature management of product during transport.

Currently, <659> and <1079.2> do not contain allowable excursion limits for products that are marketed in the range of 15° C to 30° C (i.e., climate zone IVb). The need to establish these excursion limits was identified by USP and is being analyzed by the USP Packaging and Distribution Expert Committee.

Considering that proper implementation of good distribution practices can strengthen supply chains, USP is planning to develop education programs, webinars, and other activities to be applied in Brazil and other climate IVb regions in response to these insights shared by participants during the workshop.

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ATTACHMENT I - Questions & Answers

The questions below were answered live by speakers during Q&A session of the workshop.

1. ***What do the USP-NF General Chapters with numbers above and below 1000 mean?***

Dr. Desmond Hunt: It is a hierarchy proposed by USP. It establishes which chapters are compulsory and which are not. Those numbered below 1000 are compulsory, while chapters numbered above 1000 are traditionally informative, guides. However, regulators define which chapters will be treated as compulsory, even if they are numbered above 1000.

2. ***How can people comment during the public consultation phase regarding the new USP-NF General Chapters?***

Dr. Desmond Hunt: The first way to be updated on new chapters and monographs at USP is to follow the Pharmacopeial Forum, which is an open access journal published bimonthly. It is by following what is being published for public consultation that stakeholders can effectively have their voices heard through their contributions and comments on the proposed compendial text.
Another possibility to engage with USP is to participate in Expert Panels and Experts Committees, to effectively write the chapters".
Questions or contributions related to Packaging and Distribution matters can be sent to Dr. Desmond Hunt via email: dgh@usp.org

3. ***Is there any guide to direct severity and impact scores for risk analysis in distribution, transport?***

Dr. Glaucia K. Braga: Stakeholders perceive risk differently and the analysis may vary depending on this perception. Any risk analysis tool (including ICH Q9 – Risk Management) has a qualitative component that arises from the knowledge that the team and organization have. Thus, it is suggested that the company brainstorm with its team, preferably on the same day, to establish and calibrate the scoring criteria of a tool chosen for risk analysis. With this, the risk analysis will be based on relevant information and knowledge that the organization has. Therefore, it is not appropriate to follow the risk analysis that already exists in one organization and used in another.

4. ***For a product with controlled temperature in storage and transport, and whose transport takes 8 days, how should the MKT be calculated? Should the company take into account the time it was stored, or should it calculate the MKT considering the 8 days of transport?***

Chris Anderson: The MKT must be calculated for the days that the product was in transport (8 days), so that this stage can be evaluated. Calculating 30 days using data from storage could mask the impact. If the excursions are outside acceptable limits, it is necessary to open CAPA (corrective and preventive action) so that the organization can

contact the manufacturer and request stability data that can support the evaluation of the excursion.

5. ***What if the manufacturer doesn't provide stability studies?***

Chris Anderson: The company can claim that without this information, the product will be discarded, which will impact the end customer, since they will be left without the product. About 40% of manufacturers provide stability data if there is adequate product monitoring. However, if the manufacturer does not share the stability studies, there is nothing to be done.

6. ***What is your perspective on MKT adoption?***

Dr. Lauro Moretto: It is necessary to know the MKT for Brazil. USP is dedicated to studies for climate zone II, being necessary that ANVISA together with the Brazilian Pharmacopeia conduct studies for the Brazilian climate zone, which is IVb. The MKT used by the ICH was defined only for climate zone II, and there is an urgent need to establish MKT for all other climate zones. *

**NOTE: The organizing authors of this technical report emphasize that the calculation of MKT is not exclusive to a climate zone, in addition, USP is not dedicated to conducting studies for a specific climate zone. Finally, USP clarifies that General Chapters <659> and <1079.2> do not establish permitted excursion limits for products that are marketed without temperature control in the range of 15°C to 30°C, which is the temperature range commercialization of products in Brazil, whose stability was challenged for climatic zone IVb. To understand how USP will be addressing with this demand, see final remarks.*