DRUG PRODUCTS

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National Health Surveillance Agency

GUIDANCE ON THE QUALIFICATION OF TRANSPORTATION OF BIOLOGICAL PRODUCTS

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GUIDANCE ON THE QUALIFICATION OF TRANSPORTATION OF BIOLOGICAL PRODUCTS

This Guidance expresses Anvisa's understanding on the best practices relative to procedures, routines and methods considered as suitable to the compliance with technical or administrative requirements demanded by law. It does not grant or create new obligations, and should be used by public and private agents as reference for legislative compliance.

Alternative approaches are possible, in such a way that non-compliance does not characterize health infraction, or constitutes reason for denying applications, provided the requirements demanded by law are complied with, even if through other manner than that one provided in this recommendation.

Recommendations contained in this Guidance are effective as from the date of their publication at Anvisa's Website.

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1. SCOPE

This guide has as main purpose to guide the transportation qualification activities of active biological inputs, bulk biological products, biological products in their primary package and finished biological products, establishing minimum requirements necessary to be observed for this purpose.

This document is not intended to discuss the aspects related to the Good Distribution and Storage Practices, verified during a quality audit, even though some concepts are applicable in both cases.

Subjects concerning storage procedures will not be discussed, but rather only those related to transportation.

This guidance should not be adopted as regulation, therefore, its compliance is not compulsory by the regulated sector. Each company should evaluate the guidance content and check its application. In addition, the Health Surveillance should demand the compliance of the guidance content by companies.

2. INTRODUCTION

Biological drugs are frequently formed by highly complex protein molecules, whose biological activity is dependent on their structure integrity. Both the chemical and the physical integrity can contribute for an activity loss. Chemical instability arises from a modification in the covalent bonds, while the physical instability originates when the non-covalent strengths, which maintain the secondary and tertiary protein structures, are broken. Physical instability can be minimized with a special care in storage and transportation. Usually, to avoid the physical instability, these products are maintained under controlled temperature.

The cold chain includes all the storage and transportation facilities, necessary for shipping a product that requires refrigeration, from the manufacturer to the end user.

A major concern of the pharmaceutical industry and the regulatory authorities is to assure that the drugs products are delivered to the patients with no harm of their therapeutic properties. An increasingly larger number of therapeutic products developed by the industry of biological products (vaccines, biotechnological products, among others) requires forms of transportation with controlled temperature. It is frequent to occur delays during the transportation, putting the product quality at risk when the transportation times and the temperature control cannot be maintained. In these cases, the product can present a temperature excursion.

The thermal effect adverse to the protein structure can vary from product to product. Some vaccines, for instance, are not resistant to freezing, while other vaccine classes are maintained stable. In general, lyophilized products are not affected adversely by the freezing.

The effect of high or low temperatures in the physical and chemical stability of the drugs is well known. However, high temperatures can also cause an adverse effect in some formulations, such as for example, the separation of emulsions and sedimentation of active ingredients in suspensions.

For the biological products, storage and transportation temperatures are extremely relevant for the product quality maintenance throughout its shelf life. Even though the storage conditions are relatively constant, the distribution environment can vary a lot, especially when the drug is transported between different climatic zones. There are significant variations also depending on the season.

In a simple way, the transportation chain involves the direct shipment from the manufacturer to the client or end user. In a more complex manner, the transportation chain involves different storage and transit sites, including airports, ports, warehouses, in addition of different transportation methods. All these variables have a great influence in the transportation chain.

To minimize the temperature ranges during the transportation, special cares should be taken. The main tool used for this purpose consists on qualifying the cold-chain transportation systems. The main purpose of the qualification is to show the robustness of the transportation systems used, leading to a reduction in the temperature excursions, which can occur during transportation.

3. LEGAL GROUND

Currently, the Brazilian legislation for the registration of biological products, the RDC no. 55/2010 requires, as per lines a and b, of the item X, of the article 31, the companies to submit the transportation chain validation.

For this transportation validation, it is necessary to submit the qualification of operation and performance of the systems to be used for the international and national transportations of the active ingredient, of the bulk biological product, of the intermediate biological product, of the biological product in its primary package, of the finished biological product, of the diluent and of the adjuvant (in case of vaccines).

The transportation system qualification cornerstones are the performance qualification and operation qualification of the system to be used for the transportation of the biological products.

In addition to have the adequately qualified transportation system, according to the product stability characteristics, every transportation of a biological product needs to be continuously monitored, during the import process, as for transportation temperature maintenance. These requirements are established in the article 1 of the RDC no. 38/2010, which amended the paragraphs 5 and 6, of the article 3 of the RDC no. 234/2005.

The importing company should have continuous temperature records of the transportation chain, which prove that the product was maintained within the stated transportation and storage conditions. The temperature records should identify the product name, batch number, time and date of shipping and receipt.

4. VALIDATION X QUALIFICATION

Historically, the terms validation and qualification have been used in an interchangeable manner by the cold chain industry. In this guidance, the qualification and validation concepts defined in RDC no. 17/2010 are used.

The qualification comprises the set of actions performed to certify and document that any facilities, systems and equipment are properly installed and/or correctly work and lead to the expected results.

Validation is a documented act that certifies that any procedure, process, equipment, material, activity or system really and consistently leads to the expected results. In addition, the term validation is used for processes, methods and systems for which the conditions can be controlled in the real world.

Therefore, the transportation processes can be qualified instead of validated, once it is not possible to control, in the real world, all the parameters that can affect the transportation process (for instance, weather conditions, delays caused by customs and traffic, mechanical failures, etc.).

While the qualification process is used to provide, with high level of assurance, the result that the process is reproducible under predetermined variable ranges, validation is used to describe how a system will behave under highly controlled conditions.

Even though the RDC no. 55/2010 uses the term “transportation validation”, in this guidance, the term “transportation qualification” will be used, based on the above-described justification.

5. GENERAL CONSIDERATIONS

All individuals and companies involved with the transportation activities have the responsibility to assure that the adequate transportation conditions are maintained, from the exit of the manufacturing company to the delivery to the final client.

Transportation of biological products should be made in such a way to not adversely affect their quality, always avoiding the temperature excursions.

The temperature in which the biological product should be transported is that assuring the product quality maintenance, proved by the submitted long-term stability study. Transportation should not be performed in situations other than those shown in the approved long-term stability study. The company can predict temperature excursions along the transportation, for limited times, provided the same has performed stress stability studies, which support the intended excursions.

It is understood by biological product transportation all the necessary activities for sending the product from the manufacturer company to its final destination, such as, for example, clinics, hospitals, distributors, among other facilities. In case of imported products, this activity also includes the transportation of the exporting company until the importing company.

Transportation of the active biological input, bulk biological product or biological product in its primary package is defined by all the transportation activities necessary for sending the product from a manufacturing site to the site responsible for manufacturing of the subsequent step.

More adequate transportations systems should be chosen to protect the productions from the more extreme temperature conditions, which can occur along the year in the transportation route to be qualified.

The transportation process should not compromise the integrity and quality of the products. Designs of the packaging material and of the transportation system should be adequate to prevent a physical damage to the drug during the transportation, as well as a possible contamination.

As provided by RDC no. 55/2010, for registration purposes, the transportation procedure qualification is formed, mainly, by the performance qualification and operation qualification steps of the transportation system to be used.

In addition of having the adequately qualified transportation chain, the entire import of a biological product should be monitored as for the storage temperature maintenance. Additionally, it is recommended the temperature monitoring during the transportation of biological products in national territory.

6. TEMPERATURE MONITORS

Electronic temperature monitors are equipment able to store data for long periods, creating continuous history for issuance of non-editable daily reports. Data sampling interval is adjusted by the used as necessary.

The temperature monitors should be calibrated periodically to assure that the same will operate within the manufacturer's specifications. Monitors should never be used without the proper calibration or with the expired calibration. Monitors should be located as close as possible from the product, as tested in the qualifications.

Electronic instruments, calibrated in the use range, with minimum accuracy of ± 0.5°C and minimum resolution of 0.1°C, should be used.

All the monitors should be able to record the temperature every time interval. For this purpose, the electronic temperature data loggers are normally used.

In the qualification process, the number of temperature monitors to be used will depend on the loading size and they should be carefully placed to assure that, in all the load parts, the temperature is maintained acceptable. The number of temperature monitors to be used during routine transportation should be determined based on the results obtained in the operation and performance qualifications.

Chemical monitors have their principle of operation based on the color change or indicator appearance, through an induced chemical reaction or phase change, certifying the product exposure at temperatures out of the established storage limits. However, these monitors do not allow data collection and, thus, its history. In general, they do not show with precision the indication of the exposure time accumulation at a determined temperature. Therefore, the chemical temperature monitors should not be used for the purpose described in this guidance.

Some examples of monitoring devices for comparison of the benefits are described in Table 1.

Table 1. Examples of monitoring devices to compare benefits.

Types of Monitors	Benefits	Risks/Advantages
Monitors with graphic records (paper strips)	1. Graphic record in paper strip as document for file.	1. Low accuracy; 2. High risk of losing the record, light sensitivity; 3. Sensitive to vibrations; 4. Difficult interpretation; 5. Does not allow electronic record. Only in paper strip.
Chemical monitors	1. Small device; 2. Lower cost; 3. Easy to handle.	1. Does not allow continuous record. Without information about the duration and occurrence of temperature excursion; 2. Does not allow data collection; 3. Subjective interpretation; 4. Without single ID (identity); 5. Does not allow reuse.

Electronic monitors	1. Accuracy of the acquired data; 2. Documentation with single ID; 3. There can be reusable or single-use devices; 3. [sic] Allows data collection and continuous record; 4. Possible data analysis through software; 5. Objective interpretation; 6. Diversity of applications and sizes.	1. It may require dedicated IT equipment; 2. Higher complexity in handling; 3. Higher cost.

7. TRANSPORTATION SYSTEMS

The transportation system type to be used should be decided according to the loading size, the product nature and the risk presented by the exposure to high and low temperatures, by the temperature fluctuations and by the exposure time of the system to the adverse conditions.

The systems used to pack products requiring maintenance of a certain temperature during the transportation should be divided in two groups: active systems and passive systems.

The active systems are those with active temperature control, such as for example, the containers cooled for air and maritime transportation and the refrigerated trucks.

These systems are controlled by thermostat and normally use ventilators, dried ice or an electrical refrigeration system and are fed by an external energy source.

They are systems that use electricity or another fuel source to maintain a controlled room temperature within the isolated system, under thermostatic regulation.

The passive systems are those without active temperature control, such as for example, thermally isolated containers, made of polystyrene or polyurethane, with cooling material.

These are systems able to maintain a determined temperature range within an isolated system, without thermostatic.

8. USER REQUIREMENTS (ROUTES, TEMPERATURE PROFILE, TIME)

User Requirement Specification (URS) is a document that should define the necessary requirements in a detailed and consistent manner to comply with a qualification project, describing what it is wishing to perform with it. These requirements should be written under the user's viewpoint, without defining their functionality. The approval of this document should be assigned to those in charge for the Quality and/or Distribution. At the company's discretion, this information can be contemplated in the study design or operation qualification.

8.1. REQUIREMENTS FOR AN URS

8.1.1. ROUTE CHARACTERIZATION

Route is the detailed mapping from the origin until the destination, considering all the logistical knots and the type(s) of transportation, as well as the time of each step.

The characterization of the routes is one of the require elements, along with the other logistical elements for the temperature profile definition. In addition, this will serve to develop the transportation system and to conduct the qualification testing.

8.1.2. VERIFICATION OF THE ENVIRONMENTAL CONDITIONS

Considering the origin, destination (clients) and/or the main logistical knots, the environmental conditions are verified for each period defined for the temperature profile (e.g.: Summer and Winter). To do this, it can be based in any survey performed by the company, or use official meteorological sources.

8.1.3. DEFINITION OF THE WORST CASE

In addition to the environmental conditions, the definition of the worst case should also take into consideration the route variables (duration, distance) and transportation steps (as per the example of table 2). The worst case conditions can be used to contemplate less critical routes.

8.1.4. DEFINITION OF THE TEMPERATURE PROFILE

With the times of each step and maximum and minimum temperatures, for the different periods, the temperature profile is defined. It is recommended to submit this result graphically.

The URS definition, including the temperature profile, is necessary to conduct qualification tests. Each organization or company should define its temperature profile, once that the abovementioned characteristics vary according to the route used.

The temperature profiles can be defined through the revision of environmental history data, taking into consideration the following parameters:

- Origin, destination and along the transportation routes (loading and unloading sites) temperatures;

- Seasonal temperatures (Summer and Winter);

- Duration, temperature and location of the several handling points and stop along the routes (airport / port, intermediate storages).

Other necessary information, such as the time and distance between cities, duration of flights and temperatures (maximum and minimum) in the several cities where the deliveries take place, can be obtained along with official sources (National Institute of Meteorology, Infraero, among others) or in field data.

Historical data of route temperature should be considered, in order to evaluate the uniformity of the maximum and minimum temperatures recorded and avoid mistakes from an evaluation based on point data.

Table 2. Temperature Profile Examples (Summer).

Transportation Steps	Summer	
	Duration (hours)	External temperature (ºC)
Preparation and issuance	4 h	25 ºC

Road Transportation until airport Loading Airport	16 h	35 °C
Air Transportation	16 h	25 °C
Unloading Destination Airport and Road Shipment until the Destination	12 h	40 °C

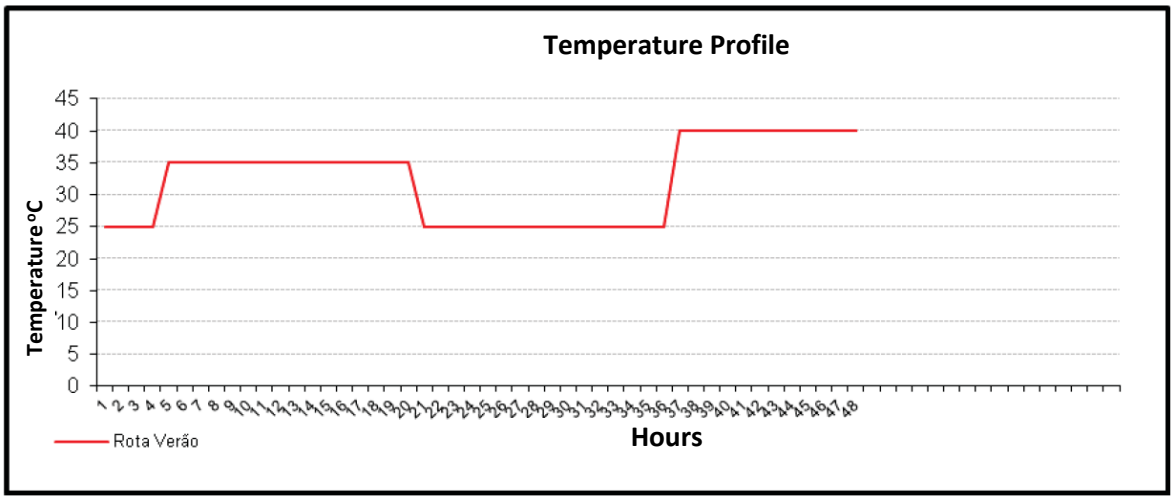

Figure 1. Summer Route: 4h at 25 °C / 16h at 35 °C / 16h at 25 °C / 12h at 40 °C.

The same rationale should be used for the definition of the temperature profile of the winter route.

9. TRANSPORTATION SYSTEM QUALIFICATIONS

The RDC no. 17/2010 defines qualification as being the set of actions performed to certify and document that any facilities, systems and equipment are properly installed and/or work correctly and lead to the expected results.

All the qualifications should always be performed following a pre-approved protocol. This protocol should be well detailed, describing the types of transportation (air, maritime, land, etc.) necessary throughout the route and specifying in which conditions occur (refrigerated truck, for example) and for how long.

There should be the description of the storage of load and of the auxiliary materials (cooling material, for example) within the transportation system used. Presentation of pictures and diagrams can be a useful tool in the understanding of the configuration of the materials within the transportation system.

The type of cooling material used should be informed, as well as its location in the transportation system and the quantity to be used. The choice of the cooling material should be performed with criteria. In some cases, such as for example, when a product is denatured by freezing, direct contact of the cooling material with the product should be avoided, using adequate for this purpose. The use of cooling material should not affect adversely the quality of the product and of its primary and secondary packages.

The company should detail how the summer, winter and mixed profiles were determined, according to the user's recommendation. The historical meteorological conditions can serve as base for this evaluation.

It is recommended that the company maintain in its files, the calibration certificates of the temperature monitoring devices, informing the date of the last and of the next calibration. Location and justification for the position of these devices in the transportation system should be informed.

The qualification protocols of the transportation system can vary according to the system type of chosen transportation. In general, the passive systems are more susceptible to the thermal variations than the active systems of transportation. However, the qualifications should be performed in both cases. The acceptance criteria for each qualification protocol should be established.

The particularities of each system should be observed. For example, for an active energy-depending system, the behavior during an energy drop should be tested.

The results obtained during the qualifications should be described in the form of a report. This report should not be restricted only to submit the results; they should be largely discussed, using bibliographical references, whenever possible.

In the case of the transportation systems, generally three types of qualification are performed: design, operation and performance. The design qualification is not required by the RDC no. 55/2010. However, when relevant, the companies can submit it along with the transportation qualification documentation.

It is recommended that the protocols and reports are issued for each step and the next step can only be started after the conclusion and approval of the previous step. For example, the Performance Qualification tests can only be started after the issuance and approval of the Operation Qualification report.

Maintenance of the "qualified" status should be made through periodical evaluation. A requalification can be necessary when change of any item that impacts the qualified system is performed, such as for example, the type, quantity and position of the cooling elements, significant route change, modification of the minimum and maximum loads, transportation system change, in addition of other relevant modifications.

9.1. DESIGN QUALIFICATION

The design qualification is performed to assure that the functional requirements of the proposed transportation system are complied with. This qualification should be performed before the performance and operation qualifications.

The parameters evaluated in a design qualification usually include:

- process duration;
- defined environmental temperature profile;
- location and quantity of the cooling material or of the conditioned air system;
- load configuration in the transportation system;
- location of the equipment responsible for monitoring the temperature;
- type of transportation system used (isolated or not, passive or active);
- minimum and maximum thermal mass.

One well-defined design qualification and with satisfactory results assures a high trust for the operation qualification.

9.2. OPERATION QUALIFICATION

According to the RDC no. 17/2010, an operation qualification is the set of operations that establishes, under specified conditions, which the system or subsystem operates as predicted, in all the considered operational ranges.

The operation qualification is a simulation of the worst conditions that can occur in a real transportation.

The tests performance should occur in environments of controlled temperature, such as for example, in climatic chambers. When it is not possible or applicable the operation qualification performance in environments of controlled temperature, such as for example, for some active systems and cooled trucks, the company should submit a technical justification and the rationale of the chosen approach.

This qualification can be performed with the product or with representative samples of the product, provided the thermal mass is preserved. Rationales with the worst case can be used to justify that a qualification contemplates other products, provided that justified by the thermal mass. To exemplify, when the product to be transported is a lyophilized powder in bottle, empty bottles can be representative. When the transportation is relative to bottles containing a determined content of injectable solution, bottles filled with placebo or water can be representative, provided the filled volume is representative of the product volume.

Specifically for active systems, the operation qualification can be performed with the configuration of minimum thermal mass and a higher volumetric occupation of the container space, which represents the airflow configuration with higher interruption, being this scenario considered a worst case. However, the operation qualification of the active systems can be product-independent.

This qualification can be performed simulating the worst conditions expected for the real transportation, in such a way to have a safety range for any unforeseen event that can occur during the transportation.

The company should show that the transportation system is able to maintain the product storage temperature, without temperature excursion, in each tests situation, for a time longer than the predicted one for the real transportation.

If the company plans a temperature excursion in the qualification protocol, it should inform the maximum time and the higher temperature to which the product can be exposed without its quality being committed, according to the specifications approved in the registration. In these situations, the completed stress stability studies should be submitted, as provided by RDC no. 50/2011, in order to support the proposed temperature excursions.

Temperature recorders should be used in sufficient quantity for mapping of the transportation under qualification. Thus, the company has how to evaluate what are the critical points of the transportation system, more susceptible to the temperature variations, justifying the choice of the points to be monitored in the performance qualification and during the real transportation.

The worst case loadings should be challenged, since the thermal mass quantity can influence in the internal temperature maintenance.

The external temperature should be monitored, in such way that the situations of more critical temperatures of the route to be used are simulated. For example, in the case of an import of the North Hemisphere, winter is usually stricter than the summer, and the contrary occurs for the South Hemisphere. However, for the sending of loads from the North Hemisphere to Brazil, the winter profile should be similar to that of the country of origin and the summer profile should be based on the higher temperatures of this time in Brazil. The company can also test a mixed profile, considering a part of the time in the winter condition and another part of the time in the summer condition, simulating the worst case, which is the shipment during the months from December to March.

It is recommended to record the temperatures (both external and internal) in a maximum interval of 30 minutes, for purpose of this qualification.

If, during the transport, opening and closure activities of the transportation system were necessary, as well as the cooling material replacement, these should be included in the qualification protocol.

A sufficient testing number should be performed to assure the robustness of the results. Normally, three simulations in each scenario (loading and external temperature profile) is the recommended number for preparing the operation qualification protocol.

Vibrational and shock tests can be planned as additional evaluations for the transportation system operation qualification.

9.3. PERFORMANCE QUALIFICATION

As provided by RDC no. 17/2010, a performance qualification is the documented verification that the equipment or system presents consistent and reproducible performance, according to parameters and specifications defined, for extended periods. Therefore, the performance qualification of a transportation system consists on consecutive shipments of the product (or of representative product samples) in real conditions, to show that the process is effective and reproducible.

Usually, the qualification is performed using typical loading configurations of the own product. In some situations, the company can perform the different transportations predicted by the qualification protocol with different loading configurations, to verify if, in real conditions, the temperature is maintained controlled in worst case loadings.

It is recommended that the shipments are performed with the product. However, when not possible, the shipments can be performed with representative product samples, as well as it occurs for the operation qualification.

When possible, the shipments for purposes of this qualification should occur at the time of the year where the route temperature is more critical.

The internal temperature monitors should be located at those points evaluated as more critical during the operation and design qualifications, according to the load quantity and system volume. The external temperature should also be monitored throughout the transportation, for at least one monitor. As per the document ASTM 3103 – Standard Test Method for Thermal Insulation Performance of Distribution Packages, it is recommended the data record interval between 10 to 30 minutes for both temperatures.

The type, number, size, location and quantity and storage conditions of the cooling material used in this qualification should be the same used in the design and operation qualifications.

A sufficient number of tests should be performed to assure the robustness of the results. Usually, three shipments are the minimum number considered and recommended for the preparation of the performance qualification protocol.

If there are temperature excursions during this qualification, the company should justify and submit the completed stress stability studies, as provided by the RDC no. 50/2011, in order to support the observed temperature excursions.

10. TEMPERATURE EXCURSIONS

A temperature excursion is a deviation of the storage conditions approved for a product for a determined period, either during storage or transportation.

Temperature excursions should be always avoided, due to the protein stability characteristics in front of the thermal effect. For example, temperatures below 0°C can lead to the freezing that, even for a short period, can denature irreversibly some proteins, leading to a significant efficacy loss. The same phenomenon can occur also with exposure to temperatures above the storage care.

Despite all the cares that should be taken during transportation so that the storage temperature is always maintained, sometimes, temperature excursions can occur for short periods.

All the temperature excursions should be immediately and completely investigated.

The difficulty in the evaluation of a temperature excursion lies in assuring that a determined excursion will not be able to change the product quality during its entire shelf life, determined by the expiration time.

A brief discussion of some concepts used currently for this is made below.

10.1. MEAN KINETIC TEMPERATURE (MKT)

A mean kinetic temperature is a fixed temperature calculated, which simulates the effect of the temperature variations in a determined period. The mean kinetic temperature is higher than the arithmetic mean of the temperatures and takes into consideration the Arrhenius equation.

The mean kinetic temperature can also be defined as a calculated single temperature in which the total amount of degradation in a determined period of time is equal to the sum of the individual degradations that can occur in several temperatures.

It expresses the cumulative thermal stress experienced by a product, in different temperatures during storage and distribution. However, there are restrictions for the use of MKT.

The MKT should be applied only in the cases where the scientific data related to thermal stability of the related product, used to establish the storage cares, allows temperature excursions between 25°C and 30°C. It is applicable only for products stored at room temperature, with approved storage care from 15°C to 30°C. It is not proper for products requiring storage at low temperatures, such as from 2°C to 8°C, for example.

MKT cannot be used to compensate a precarious temperature control or its lack during transportation of a drug.

10.2. ACCELERATED STABILITY STUDY

As per the RDC no. 50/2011, the accelerated stability studies are studies designed to accelerate the chemical, biological degradations or physical changes of a pharmaceutical product, in forced storage conditions. The temperature used is higher than that used in the long-term stability study.

This type of study shows the consequences of a determined temperature in the characteristics of quality of a product. However, these studies, alone, do not serve to show the impact of a temperature on the quality of a product until the end of the shelf life.

It is a model based only on the compliance with the specifications for the product in the established times. Only an accelerated stability study is not enough to support the evaluations of the temperature excursions.

10.3. STRESS STABILITY STUDY

As defined by the RDC no. 50/2011, this study is designed to evaluate the impact of short exposures to conditions beyond of those established in the product label, which can occur during transportation and/or storage.

Each stress condition imposed to the product can lead to a determined degradation level, affecting its quality. Temperature excursions next to the storage temperatures can affect the product minimally; however, any other stress condition can significantly affect its quality.

Because the stress conditions are tested and the study continues to be conducted under long-term conditions until the end of the expiration time, this type of approach is able to evaluate the impact of temperature excursions on the product quality. It evaluates the cumulative effect of the temperature excursions on the product quality.

Currently, this study is required to support in the evaluation of possible temperature excursions.

11. FINAL CONSIDERATIONS

It is essential to know, monitor, control and document the storage, distribution and transportation activities of products temperature sensitive, always searching for optimization of the cold chain.

Brazil is a country with several critical factors for transportation of drug products temperature sensitive, such as large climatic variation and territorial extension of continental proportion, added to the difficulties inherent to transportation, such as decentralization of services, goods circulation volume, transportation modal type, among other factors. For these reasons, there is a great facility in breaking the cold chain links and a vulnerability in not assuring the quality and safety of the products in the logistics operations.

With the publication of this Guidance, a higher harmonization of the concepts used for the Cold Chain and direction as for transportation of the temperature-sensitive biological products is expected.

12. GLOSSARY

Cold Chain or Cold Network: is the process included by the storage activities, storage, handling, distribution and transportation of the Temperature-Sensitive Products.

Calibration: set of operations that establishes, under specified conditions, the relation between the values indicated by an instrument or system of measurement or values represented by a materialized measure or a reference material and the corresponding values of the greatness established by standards.

Calibration Certificate: document certifying that the equipment was tested in controlled conditions and compared to established standards, thus assuring that the results measured by instruments are trustworthy.

Container: environment used for storage and/or transportation of products, and it can be refrigerated and with the controlled temperature.

Acceptance criterion: criterion that establishes the specification acceptance limits of raw materials, products or processes/systems.

Quality deviation: distance from the quality parameters established for a product or process.

Cooling Element or Material: materials used for cooling a transportation system.

Equipment: measurement instrument, set of instruments and facilities necessary for an operation.

Specification: document describing in details the requirements that the materials used during manufacturing, intermediate products or finished products should comply with. Specifications serve as base for quality evaluation.

Temperature Excursion: is a deviation from the storage conditions approved for a product, for a determined period, during storage or transportation.

Modal: type of transportation used to ship biological products (maritime, air, road, fluvial and train).

Worst case: one or more conditions that present the highest possibilities of product or process defect, when compared to the ideal conditions.

Qualification: set of actions performed to certify and document that any facilities, systems and equipment are properly installed and/or work correctly and lead to the expected results.

Design Qualification (DQ): documented evidence that the facilities, support systems, utilities, equipment and processes were designed according to the requirements of Good Manufacturing Practices (GMP).

Operation Qualification (OQ): set of operations that establishes, under specified conditions, that the system or subsystem operates as required, in all the operational ranges considered.

Performance Qualification (QP): documented verification that the equipment or system provides consistent and reproducible performance, according to parameters and specifications defined, for extended periods.

Passive transportation system: are those without active temperature control, able to maintain a determined temperature range within an isolated system, without thermostatic regulation, normally using a finite amount of cooling material.

Active transportation system: are systems that use electricity or other energy source to maintain a controlled room temperature within the isolated system, under thermostatic regulation.

Validation: documented act that certifies that any procedure, process, equipment, material, activity or system really and consistently leads to the expected results.

13. BIBLIOGRAPHICAL REFERENCES

AMMANN, C. (2011). Stability Studies Needed to Define the Handling and Transport Conditions of Sensitive Pharmaceutical or Biotechnological Products. *AAPS PharmSciTech* , pp. 1264-1275.

ANVISA. (12 de julho de 2013). Fonte: http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Inicio/Medicamentos/Assunto+de+Interesse/Produtos+Biologicos

ASTM 3103 – *Standard Test Method for Thermal Insulation Performance of Distribution Packages.*

ASTM D 4169-05_*Standard Practice for Performance Testing of Shipping Containers and Systems*.

BADURINA, G., MAJIC, Z., & PAVLIN, S. (2011). Evaluation of air Transportation under Controlled Room Temperature for Pharmaceuticals. *Traffic & Transportation*, pp. 121-130.

BISHARA, R. H. (2005). Qualification Versus Validation and Good Cold Chain Management Practices. *Pharmaceutical Manufacturing and Packing Sourcer* .

BISHARA, R. H. (2006a). Cold Chain Management - An Essential Component of the Global Pharmaceutical Supply Chain. *American Pharmaceutical Review* , pp. 1-4.

BISHARA, R. H. (2006b). The Application of Electronic Records and Data Analysis for Good Chain Management Practices. *The Journal of Pharmaceutical & Biopharmaceutical Contract Services* , pp. 1-5.

BISHARA, R. H. (2008). Good Cold Chain Practices for Clinical Trial Materials / Investigational Medicinal Products. *American Pharmaceutical Outsourcing* , pp. 1-4.

BRAZIL. (17 August 2005). RDC no. 234. Provides on the import of biological products in their primary package and the finished biological product subject to the health surveillance regimen.

BRAZIL. (December 16, 2010). RDC no. 55. Provides on the registration of new biological products and biological products and gives other provisions.

BRAZIL. (August 18, 2010). RDC no. 38. Amends RDC no. 234, of August 17, 2005.

BRAZIL. (April 16, 2010). RDC no. 17. Establishes the minimum requirements to be followed in the drug product manufacturing.

BRAZIL. (September 20, de 2011). RDC no. 49. Provides on the conduct of changes and inclusions post-registration, suspension and reactivation of manufacturing and cancellations of registration of biological products and gives other provisions.

DUTTA, S., SENGUPTA, M., DAS, S. K., & KUMAR, S. (2009). Importance of Cold Chain Management in Stability of Pharmaceutical Product. *International Journal of Pharma. Research & Development* , pp. 61-63.

EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES. (2013). Guideline on Good Distribution Practice of Medicinal Products for Human Use. *Official Journal of the European Union* , pp. 1-14.

FORCINIO, H. (2013). Seeking col-chain efficiency: medication safety and efficacy depend on maintaining products at the proper temperature. *Pharmaceutical Technology*.

GOFF, R. (2012). What Happened On The Way to Your Costumer? *Pharmaceutical Outsourcing* , pp. 1-3.

HAWKINS, J. (s.d.). *Moving to Electronic Temperature Monitoring*. Fonte: www.worldpharmaceuticals.net

HEALTH CANADA. (2011). Guidelines for Temperature Control of Drug Products during Storage and Transportation. pp. 1-9.

IRISH MEDICINES BOARD. (2011). Guide to control and monitoring of storage and transportation temperature conditions for medicinal products and active substances. pp. 1-20.

ISPE Brasil. (2013). Manual Brasileiro de Boas Práticas de Cadeia de Frio, pp. 1 – 102.

LUCAS, T., BISHARA, R., & SEEVERS, R. (2004). A Stability Program for the Distribution of Drug Products. *Pharmaceutical Technology* , pp. 68-73.

ORGANIZAÇÃO MUNDIAL DA SAÚDE. (2006). Good Distribution Practices for Pharmaceutical Products. pp. 180-202.

ORGANIZAÇÃO MUNDIAL DA SAÚDE. (2011). Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. pp. 324-372.

PARENTERAL DRUG ASSOCIATION. (2007). Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment. *PDA Journal of Pharmaceutical Science and Technology* , pp. 1-20.

REDDY, C. M., MALLIYALA, S., NARESH, Y., RAGHUNANDAN, H., & JINADATHARAYA, H. (2012). Good Cold Chain Management Practices. *Journal of Pharmacy Research* , pp. 5043-5047.

SIMONNOT, O. (2012). Monitoring Value. *Parenterals: Cool Chain* , pp. 34-36.

TAYLOR, J. (2001). Recommendations on the Control and Monitoring of Storage and Transportation Temperatures of Medicinal Products. *The Pharmaceutical Journal* , pp. 128-131.

TAYLOR, J., & HOLLOWAY, I. (2007). Transportation of Biological Products: European Regulations and Guidance. *American Pharmaceutical Outsourcing* , pp. 1-4.

TREDREE, R. (2007). The Supply Chain for Biopharmaceuticals: Maintaining the Correct Temperature. *Official Journal of the European Association of Hospital Pharmacists* , pp. 52-54.

UNITED STATES PHARMACOPEA 35. (2012). (1079) Good Storage and Shipping Practices. pp. 1-6.

VAISALA. (2012). FDA & ICH: Regulations and Standards for Temperature-Controlled Supply Chains.