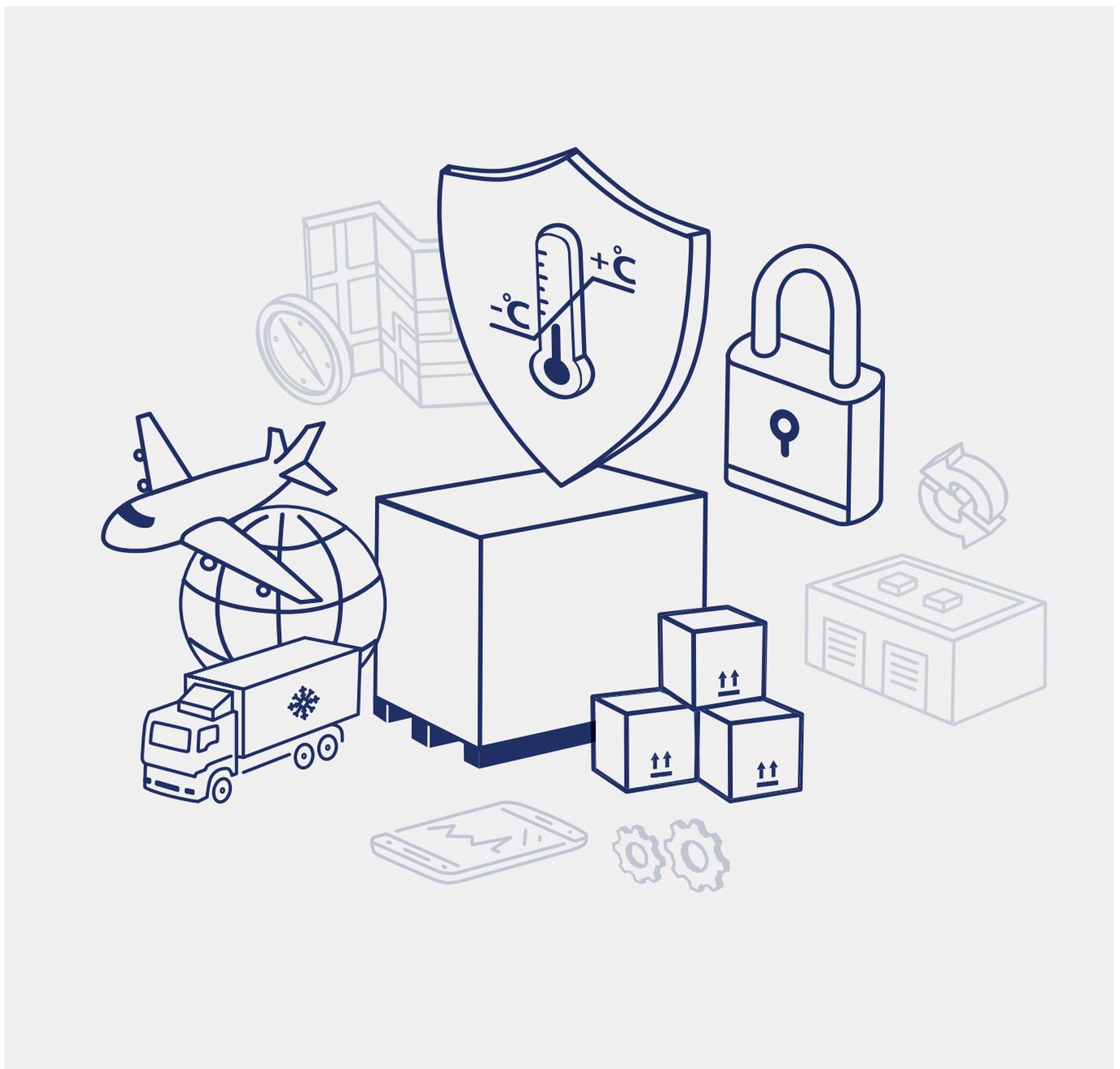


Product Safety in temperature-controlled Supply Chain

An Overview of the Challenges, influencing Factors and Solutions



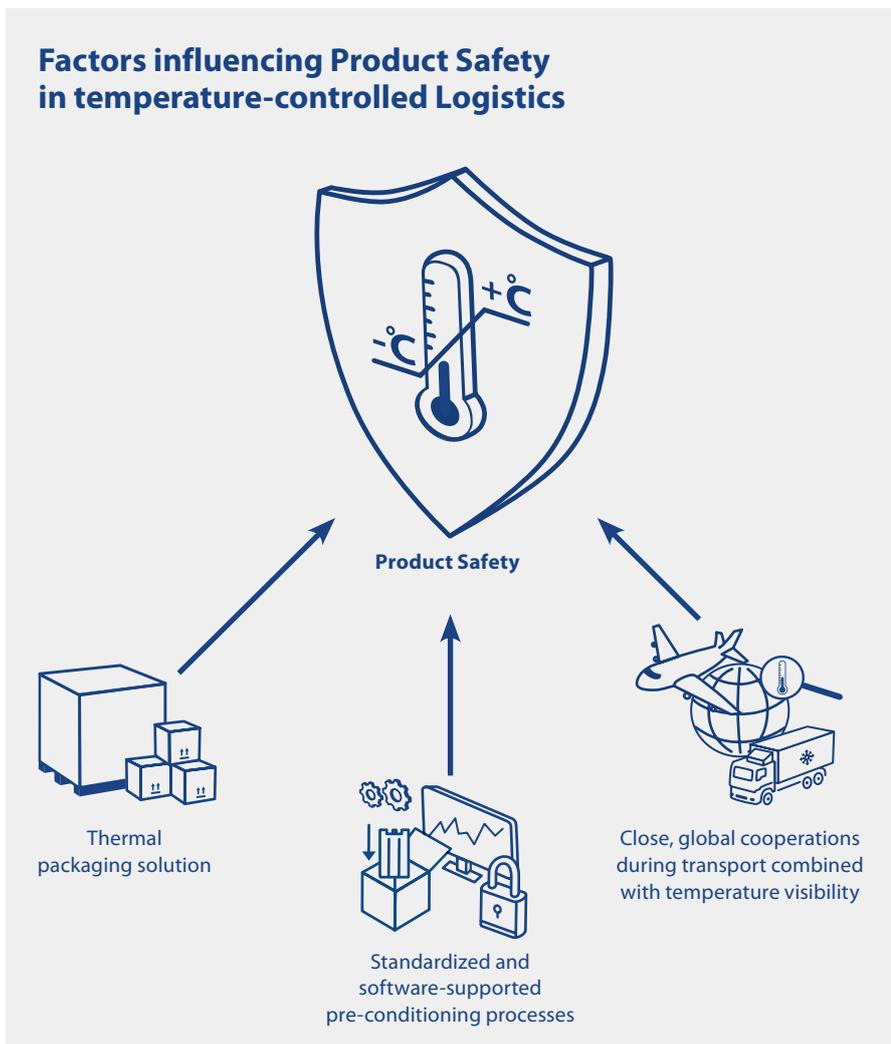
The temperature-controlled Supply Chain: a Chain with many Challenges

Temperature-controlled transport logistics poses major challenges to companies, particularly to those in the pharmaceutical and biotechnological sectors. Medicinal products, vaccines and other temperature-sensitive products must be transported within defined temperature ranges, as they would otherwise lose their effectiveness or even have harmful effects on patients' bodies. **Product safety during transport therefore plays a critical role both for the wellbeing of patients as well as for the shipper of pharmaceutical or biotechnological products.** In order to best ensure the safety of such products, there are extensive guidelines in place: **The so-called Good Distribution Practice (GDP) defines the requirements for temperature-controlled transport.** These requirements are becoming increasingly important due to the ever-more complex molecular structures of bio-pharmaceutical active ingredients, e.g. mRNA vaccines. This leads to the GDP being continually strengthened and now applies almost all over the world.



How can Risks be minimized? A brief Overview

At the end of this document, you will find a useful checklist which will help you to minimize the risk of temperature deviations.



Focus on Product Safety

Medicinal products with complex molecular structures and the proteins found within these structures are becoming increasingly valuable and increasingly sensitive to temperature deviations. For this reason, the shipper of temperature-sensitive products must pay great attention to the safety of the temperature-controlled supply chain. **Temperature-controlled transportation is mainly focused on the avoidance of temperature deviations.** Other aspects, such as protection from mechanical effects, fluctuations etc., also play a role.

TempChain

Temperature-controlled supply chain of temperature-sensitive goods, which accounts for both the positive and negative temperature ranges

Challenges during Transport

Despite careful planning, there are many uncertainties in practice. The required temperature range, the sensitivity and the value of the transported goods all affect the risk a product is subjected to. In addition, product safety can be affected by unpredictable factors during transport: weather and temperature forecasts, potential delays due to traffic jams, flight cancellations and much more. In a **lane design**, whether it is over a short distance or a long distance, these unpredictable aspects must be taken into account, in order to guarantee maximum product safety and thus compliance with the GDP. **Product safety in temperature-controlled logistics** therefore depends on **three central influencing factors**:

Lane Design

Transport planning of a temperature-sensitive product, taking all unpredictable aspects into account

- 1** The choice of **thermal packaging** and thereby also of the **packaging technology**. Safer and higher performing packaging allows more risks to be avoided at this stage.
- 2** **Preparing processes** or **pre-conditioning**: Simple, easy, fast and controlled processes, e.g. software-supported, avoid the risk of human error.
- 3** The **transport**: the faster, more direct and more temperature-controlled, the fewer unpredictable aspects can occur.

The Role of thermal Packaging Solutions

Thermal packaging has a major influence on whether the safety requirements of the Pharma Shipper, the compliance to GDP and thus patient wellbeing, can be guaranteed.

Generally, insulation plays a critical role in thermal packaging solutions, as the thermal resistance of an insulating material determines how much heat or cold penetrates inside the packaging solution during transport. The higher-performance and thicker the insulating material, the less heat exchange takes place with the surroundings. Normal insulating materials in packaging solutions, for example, consist of EPS, EPP or rigid polyurethane foams. Vacuum insulating panels are used in high-tech solutions.

Although the insulation in a packaging solution reduces heat exchange with the surroundings, heat exchange always takes place to a certain extent. Therefore, a second type of technology must be used in order to keep the outside temperature away from temperature-sensitive pharmaceutical products. Here, we distinguish between two technologies: **active and passive.**

Active Technology

In active temperature control, a **cooling or heating unit** makes it possible to maintain the defined temperature limits. If heat enters the system from outside, the cooling unit cools the products. If on the other hand cold enters the system, the heating takes effect. Alternatively, there are solutions with dry ice compartments, where the **dry ice works as a coolant**, but it must be frequently refilled during transport (re-icing).

An active system is easy to apply: the desired temperature set point must be chosen and the batteries must be charged. However, this solution also has its disadvantages. **Active solutions are dependent on battery capacity** meaning that it must be considered in advance in the lane design of a transport route whether and where the batteries can be recharged during transport. For intercontinental transport in particular, it is not unusual for several flights to be necessary in order to reach the final destination. For this reason, recharging at several of the airports involved must be planned in advance. Low battery lives, worn out batteries or a limited number of charging spots in so-called pharma-hubs additionally endanger product safety. Usually, such solutions can **only maintain internal temperatures in the range of -20 °C to +20° C**, whereby the negative temperature range is heavily limited by the ambient temperature.

Active solutions are **less energy-efficient** than passive solutions, as thermal energy is not stored directly. Energy is lost due to the conversion of electrical energy into cold or heat. A further indication is the fundamentally **lower autonomy**. Units can fail and must be serviced regularly. Active solutions also require increased **regulatory complexity with regards to aviation authorities.**

Active Technology

A cooling unit and a heater or fan in combination with dry ice allow the internal temperature to be set

Passive Technology

Passive systems do not have active components such as electrical batteries, electronics, fans or electrically powered heating or cooling systems



Active Technology

Electrical cooling or heating unit with batteries

Passive Technology

Passive systems **do not have active components such as electrical batteries, electronics, fans or electrically powered heating or cooling systems.** They are based on fundamental physical principles.

In passive solutions, **the intruding heat or cold is absorbed and stored by temperature storage elements before it reaches the product.** While a material is melting or freezing, it does not change its temperature, although heat must be supplied to melt the material or be removed to freeze it. Passive solutions make use of this effect.

In traditional passive systems, frozen water coolants are used. The variant where water melts or freezes at 0 °C is usually used for pharmaceutical products which require a temperature range of +2 °C to +8 °C. This typically leads to temperature deviations with a high risk of temperatures being too cold and thus, endangering product safety.

High-tech Solutions

These advanced passive solutions are high-performance systems which make use of insulation by vacuum insulation panels and temperature control using temperature storage elements with phase change materials.

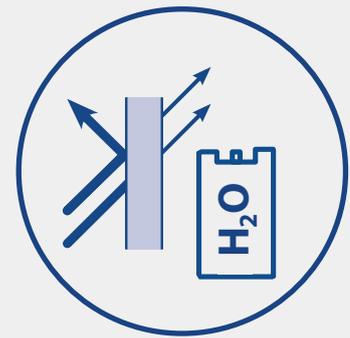
Vacuum Insulation Panels

So-called vacuum insulation panels (VIPs) are particularly noteworthy and are being used increasingly often in the field of thermal pharmaceutical packaging.

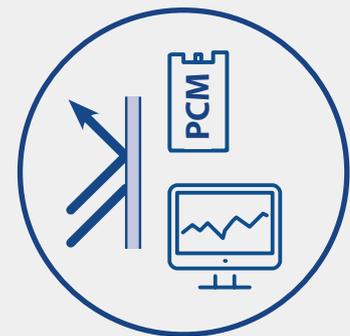
They use the same insulation principle as a Thermos flask. The thermal conductivity of a vacuum is extremely low, making the panels the ideal insulation for temperature-controlled transport containers. **The thermal insulation performance of VIPs is up to 10 times higher than that of traditional insulation materials.** 10 mm VIPs insulate approximately as well as 100 mm of EPS. This means that using VIPs allows for space-saving and nevertheless exceptionally efficient insulation, which is able to keep extreme external temperatures and fluctuations of the external temperature away from the interior of the packaging extremely well.

Temperature Storage Elements with Phase Change Materials

Phase Change Materials (PCMs) absorb heat as they melt and release it again as they crystallise and freeze. This allows the required internal temperature of a transport package to be maintained for the duration of the transport, if a material is chosen with a melting point within the required temperature range of the pharmaceutical product in question. **The va-Q-tec PCMs allow for numerous temperature ranges for transport at temperatures between -70°C and +40°C,** making them significantly superior to traditional water solutions, even in the standard temperature range of +2 °C to +8 °C.



Standard passive Technology
Normal insulation materials and water coolants



High-tech Solutions from va-Q-tec
High-tech insulation materials and temperature storage elements filled with phase change materials supported by digital processes

Qualified Performance

With va-Q-tec solutions, the combination of VIPs, PCMs, digital solutions and the TempChain Network ensures even better energy efficiency, is more environmentally friendly, and protects from temperature deviations. The technology offers **qualified performance for up to ten days without external power supplies** and provides a high level of protection against extreme temperatures and temperature deviations in comparison to active solutions, meaning it offers significantly **more autonomy**. The qualified performance in real transport can even be extended when the thermal packaging solution is stored temporarily in temperature-controlled rooms or vehicles. **With va-Q-tec products, worst-case scenarios are employed to consider an outstanding degree of safety:** the performance is measured without product load or with a minimal product load at three different worst-case positions. In reality, the external temperatures which a transport solution is exposed to are more moderate than the worst-case scenarios, which provides a further performance reserve. It can be shown that the va-Q-tec solution is superior to the active solutions in terms of performance.

va-Q-check® verified

Insulation materials can age, i.e. lose efficiency, for example when the foaming gas of a PU foam is replaced by normal air.

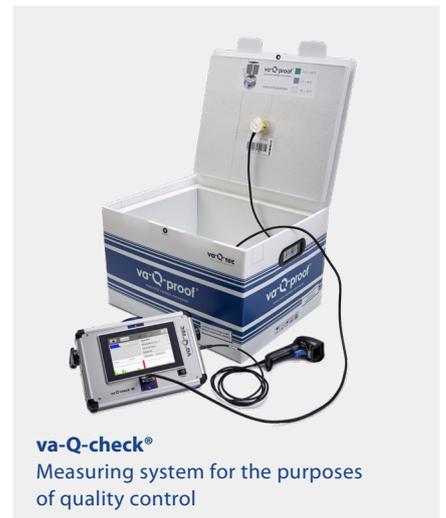
In the case of VIPs, the insulation capacity is dependent on the quality of the vacuum. For this reason, va-Q-tec has developed **the worldwide patented quality control system va-Q-check®** that enables the internal gas pressure of each individual VIP to be checked within seconds. This in turn allows va-Q-tec to check before every transport whether the vacuum, and therefore the insulation capacity, meet the quality requirements as they did on the first day after production, meaning that the vacuum can provide **optimal safety in the temperature-controlled supply chain with regards to insulation**. This unique checking system is the only option worldwide for checking an insulation material rapidly and precisely.

Hibernation

Effect when a transport solution is stored in a temperature-controlled room. If the difference between the required internal and external temperature is extremely small, the thermal packaging can be stored infinitely without any loss of performance

KelvinHours

Parameter describing the difference between the average external temperature and the required internal temperature, as well as the time for which the required temperature is maintained



va-Q-check®
Measuring system for the purposes of quality control

The Role of the Pre-Conditioning Process

If the transport solution is not properly pre-conditioned, temperature deviations may occur during transport. For example, the correct pre-conditioning of temperature storage elements, the complete charge of batteries or loading with dry ice, needs to be defined in a concrete process. However, batteries age and lose performance over time. This cannot be checked during the preparation process. **Ensuring internationally reproducible, validated processes influences product safety**, as the handling plays an advance role in the performance of the packaging solution.

TempChain Services

The va-Q-tec TempChain Service Network offers clear advantages here. In **almost 40 TempChain Service Centers** around the world, the temperature storage elements are pre-conditioned in precise temperature-controlled cooling chambers. The pre-conditioning management in these cooling chambers and approval of the cooling chamber temperatures is managed centrally by the TempChain Service Software and is constantly checked by the so-called Control Tower.

All data regarding the pre-conditioning process is digitally documented and saved in a blockchain. This works like a decentralised database, guaranteeing protection against forgery and transparency using cryptographic methods and their dispersed basic structure. With the **blockchain seal**, data can be transmitted in a tamper-proof manner. The software-validated processes and the four-eyes principle provide more product safety in the temperature-controlled supply chain.

Transparent Digitalization of Quality Control

Alongside pre-conditioning, quality control with the help of the va-Q-check® system also takes place in the TempChain Service Centers: in order to guarantee the temperature is maintained for the optimal period, the insulation of the boxes and containers is checked before they are sent onwards. Only when the transport solution has successfully passed strict checks is it approved for further transport. This patented va-Q-check process consistently checks the quality of the transport solutions and enables assurance of the **day-one validation**.



Pre-Conditioning

During pre-conditioning, the transport solutions are prepared for transport, dependent on the technology used

Blockchain Seal

A tamper-proof electronic seal based on blockchain technology. A blockchain is an encoded databank with a decentralised basic structure

Day-One Validation

Validates whether a transport solution is just as efficient as on the day it was produced

The Role of Transportation

The challenges of temperature-controlled transport are manifold. Is the destination reachable within 48, 72, 96 or even 120 hours? How much performance buffer should be integrated into the originally planned duration of transport? **Extreme weather conditions, traffic jams on route, missed flight connections or unavailable plug sockets or adapters for active cooling systems occur as sudden unpredictable aspects.** Additionally, the performance of the battery depends on the external temperature and can fluctuate accordingly.

Airlines and freight forwarders offer appropriate service models in order to minimize these risks. Their services include significantly shorter transport routes and cooling equipment at airports, as well as temperature-controlled compartments on board most flights. va-Q-tec works with **over 70 airlines and freight forwarding partners** based on the **Global Rental Agreements**, who have high-tech solutions as a **standard part of their portfolios** and can carry goods without further permits.

Even when these extra services are booked, some of the unpredictable aspects remain. These risks can be eliminated by choosing the correct packaging solutions and the appropriate services. **va-Q-tec can make a valuable contribution with its TempChain network.**

The TempChain Network provides a valuable Contribution

In order to safely transport temperature-sensitive goods, va-Q-tec offers its customers a comprehensive range of services in the field of temperature-controlled logistics. The basis for this is the **international TempChain network**, comprised of almost 40 TempChain Service Centers (TSCs). It ensures that the distance between the hubs and the shipper is as short as possible and that solutions are rapidly available all over the world. The customer receives an optimally pre-conditioned container **“ready to load & go”**, which they simply need to load their goods into.

Temperature data loggers in the transport containers supply complete important temperature data **according to the GDP requirements.** The **va-Q-nection** service offers full temperature monitoring with an interface in the TempChain Service Software. The temperature in the interior of the packaging is retrievable at any time during transport with a barcode and smart device, allowing intervention if a temperature deviation is imminent. Furthermore, immediately after receipt of the goods, the temperature data and an associated shipment report is automatically retrievable by both, the receiver and the shipper, in the TempChain Service Software.

va-Q-nection

Comprehensive temperature monitoring system in order to monitor temperatures at all times during a temperature-controlled transport

Conclusion

Optimal product safety requires avoidance of temperature deviations. **Alongside pre-conditioning and transport, the largest influence on the risk of temperature deviations is the thermal packaging itself as this allows for a high level of autonomy.** This autonomy ensures a performance buffer in case unpredictable aspects occur in transit.

The GDP specifies strict guidelines with regards to temperature monitoring during the entire delivery chain, in order to ensure the highest level of product safety. The Pharma Shipper must decide the level of safety based on product value, product sensitivity and the individual challenges posed by transport planning.

High-tech solutions offer the highest levels of autonomy due to their independence from electrical power and can achieve a vast time and performance buffer. The choice of safe packaging is thereby the best way of counteracting the unpredictable aspects of transport. With innovative vacuum insulation panels and temperature storage elements made from phase change materials, va-Q-tec manufactures innovative products to defy even the most adverse of temperature transport conditions.

With the TempChain network, va-Q-tec has additional services at its disposal which ensure an unbroken TempChain with an extremely high level of product safety. The use of digital technologies, internationally reproducible software-supported processes, the highest level of temperature visibility during transport and a global partner network ensure high product safety and overall avoidance of temperature deviations.

With va-Q-tec's innovative thermal packaging systems, GDP-compliant transport through the entire temperature-controlled supply chain, from commercial shipment to the last mile, is no longer a problem.



On the next page you will find a useful checklist which will help you to minimize the risk of temperature deviations.

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Checklist

for the Minimization of Temperature Deviations during Transport or GDP-compliant Deliveries

1. Transport Planning to determine Minimum Performance Requirements for thermal Packaging

- The temperature requirements and the value of the product are known
- The transport route is defined
- The resulting standard delivery time for the planned shipment is known
- The expected minimum and maximum external temperatures or different climate zones for the shipment have been taken into account
- All possible delays, such as traffic jams, delays in customs, missed connecting flights have been taken into account
- Options for minimizing risk and their availability have been checked and determined with the transport service provider
- An adequate performance safety buffer has been included to the packaging performance requirements to cover for unpredictable events
- The transport routes between the shipping location, airport, destination and other transition points have been kept as short as possible

2. Choice of thermal Packaging

- The performance is adequate for the standard delivery time including a safety buffer
- The performance is suitable for the temperature requirements:
 - The chosen temperature profile, according to international standards (e.g. ISTA), covers the expected transport duration and the expected climate, including the selected safety buffer
 - The qualified performance in hours according to international standards (e.g. ISTA) is available
 - The qualified performance in KelvinHours is available and takes into account the expected difference between the external and internal temperature
 - According to worst-case scenarios
 - Without payload or with minimum payload
 - With at least three different sensor positions
 - The sensor positions should not be on the worst case positions only (not at the generator, not at the payload, not directly at the temperature storage element), they should also give a good overview about the temperature distribution in a box (3D mapping)

- Aging effects have been taken into account in the performance, making the results applicable to each individual container or box
 - With regards to insulation material
 - With regards to temperature control (e.g. aging of batteries, coolant, ...)
- The quality of the insulation is verifiable and proven
- The temperature management (via cooling units/heaters or phase change materials) is verifiable or reproducible
- The internal temperature or the required temperature range is easy to verify without opening the packaging
- The thermal packaging is available globally with short transport routes

3. Safe Preparation Processes and Process Monitoring

- Pre-conditioning occurs identically independent of the time of year
- The pack-out is independent of the time of year
- The system comprises a small number of individual components and enables simple, intuitive handling
- The preparation processes are globally consistent
- The processes are safe, audited and transparent
- The processes are software-controlled and are consistently monitored centrally and by experts
- Safety mechanisms (e.g. four eyes principle) are implemented in the processes
- The process data is documented, stored in a tamper-proof manner and made available in an encrypted form (blockchain technology)
- The set temperature range can be easily checked (e.g. using a colour code or a temperature display)
- The pre-conditioning can be checked (e.g. with transparent shells, visible PCM)
- The quality of the materials can be easily monitored (insulation check, e.g. pressure test for vacuum insulation panels, quality of battery)