Scientific Standards for Ambient Temperature Profile Development:

The creation of standard ambient temperature profiles for insulated package development and an analytical process for profile comparison

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ABSTRACT:

Storing and shipping highly temperature-sensitive drug products requires sophisticated packaging to ensure that the product remains safe and viable — from the manufacturing plant to the end user. Incorporating the appropriate ambient temperature profile into the design of this packaging is critical to maintaining the temperature control that these products require.

ThermoSafe Brands has developed two unique and comprehensive distribution temperature profiles for use in the design and development of temperature assurance packaging, as well as a proprietary analytical method for comparing ambient temperature profiles. The ISCgold™ and ISCsilver™ Ambient Temperature Profiles allow users to choose a design profile based on their specific shipping needs and criteria.

- The ISCgold™ Ambient Temperature Profile has been developed to meet some of the most extreme temperature conditions known to exist in the transport and distribution of drug products.
- The ISCsilver™ Ambient Temperature Profile has been developed to provide protection to packages under moderate or temperature-controlled distribution conditions.

Rather than a simple snapshot from limited data that was taken over a brief period of seasonal extremes, these two profiles are based on the analysis of multiple sources taken over multiple years, from various countries, lanes, and seasons.

Comparative analyses have been performed on both profiles, supporting with a high degree of confidence that they meet or exceed known industry standard profiles, as well as an overwhelming majority of custom profiles that have been developed and used in the industry in the past decade.

<table>
<thead>
<tr>
<th>Primary Application</th>
<th>ISCgold™</th>
<th>ISCsilver™</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Shipping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Value Product</td>
<td></td>
<td>For products of high monetary value, such as an oncology product.</td>
</tr>
<tr>
<td>Strict Temperature Control</td>
<td></td>
<td>For products that need to maintain specific temperature control, i.e. 2-8ºC for vaccines.</td>
</tr>
<tr>
<td>Clinical Trial Shipments</td>
<td></td>
<td>High risk of losing time or monetary investment.</td>
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<tr>
<td>Controlled Temperatures</td>
<td></td>
<td>Customer has made arrangements for product to be protected during the path (refrigerated trucks, etc.)</td>
</tr>
<tr>
<td>Overnight Delivery</td>
<td></td>
<td>When the risk is low that product will be exposed to extreme temperatures.</td>
</tr>
<tr>
<td>Rx Distribution</td>
<td></td>
<td>When the risk is low that product will be exposed to extreme temperatures.</td>
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**DISCUSSION:**

**The Challenge of Developing Ambient Temperature Profiles**

The design and development of insulated packaging systems for managing temperature-controlled product during transport and distribution requires a thorough knowledge and understanding of the distribution environment through which the package must travel. As a result, temperature profiles can be developed that accurately represent the expected ambient temperature exposure that these packages experience during shipment.

There are numerous methods for developing ambient temperature profiles. They range from empirical analyses, where the distribution lanes are mapped and monitored for temperature data and other relevant environmental hazards (i.e. humidity, light, vibration), to theoretical models, where rationale is determined based on geography, historical weather data, or other general information about the distribution environment. Profiles may differ as a result of geography, transportation lanes, handling practices, mode of transport, and transportation duration. Currently, there is no standard for the development of ambient temperature profiles.

It is a regulatory imperative that drug applicant license holders document their supply chain processes and employ, or delegate to their supply chain partners, current best practices for the distribution of their drug products. This includes sound rationale and justification for the use of ambient temperature profiles within the distribution environment.

Organizations may choose to incorporate an existing industry profile, work with a supplier’s profile, or develop their own profile. This decision is critical to the package design, as the more challenging the profile, the more robust and expensive the package.

**Profile Development**

In cases where an ambient temperature profile has not yet been developed or a company does not have the resources to do so, a standard profile can be used as a starting point. Data should be collected on the packages shipped to determine if actual temperature conditions in the field shipments match the standard profile selected for that product. If variances occur, the profile and packaging should be altered accordingly.

The performance of a temperature-controlled package design is limited by the level of stress exposed through the ambient temperature profile. In many cases certain assumptions must be made in the decision process, and the final profile selection is generally predicated on risk management. However, organizations frequently have to revisit their profile decisions and redesign their packages after experiencing unexpected failures in the field. This can have regulatory implications and the potential to affect the quality of the drug product.
Choosing the Right Standard

ThermoSafe Brands recognizes the importance of incorporating an accurate ambient temperature profile. Some organizations do not have the resources to develop their own profile or possess the required experience to accurately assess whether an industry profile or a supplier’s recommended profile is suited for their application, particularly given the complexities of international transport and distribution of healthcare products.

This decision is further complicated by the lack of a true industry standard. While the International Safe Transit Association (ISTA) has published several profiles over the years (5B, 7D, 7E), these profiles speak in terms of generalities and are only representative of specific distribution practices, modes, and lanes. They serve as a good starting point for organizations that have not characterized their own distribution environments, but are not generally accepted among global regulatory authorities as a means of justifiable documentation of distribution lanes.

To address the complexities of global distribution and the lack of a global industry standard to assess widespread applicability of standard industry temperature profiles, ThermoSafe Brands has developed a set of ambient temperature profiles, called ISCgold™ and ISCsilver™, that are suited for nearly all applications.

ISCgold™ and ISCsilver™ Ambient Temperature Profiles

The ISCgold™ Ambient Temperature Profile was specifically developed to stand among the most rigorous profiles in the industry. Its range is inclusive of temperatures used in standard profiles, such as ISTA 7D and 7E, in addition to more than 90% of ambient temperature profiles published by suppliers and manufactures over the past decade.

The ISCsilver™ Ambient Temperature Profile is a more moderate profile representative of less extreme climates, express air transit, well-controlled distribution environments, or conditions where packages are generally not as susceptible to exposure to extreme temperatures. The ISCsilver™ Ambient Temperature Profile is comparable to existing ambient profiles such as the ISTA 7E and other profiles published by suppliers.

In addition, ThermoSafe Brands has developed a proprietary scientific process, called the ISC Ambient Profile Assessment Model, for comparing data from one profile to another.

This document further describes the methodology and rationale for developing and analyzing both the ISCgold™ and ISCsilver™ Ambient Temperature Profiles.

A New Vaccine Ships Safely and On-Time for Flu Season

When a large biotech company was ready to begin shipping its new, innovative flu vaccine to distribution centers around the United States, they needed the product to maintain strict temperature control within a very limited range. Excursions above or below the range would render the vaccine ineffective. The company did not have an in-house universal packaging solution to cover the extreme range of temperatures that the package would be exposed to during shipment and turned to ThermoSafe Brands for help. ThermoSafe Brands provided a Certis™ Qualified Shipper, a solution that ensured ultimate protection for even extreme shipping conditioning and offered a quick off-the-shelf shipping solution in time for flu season. The successful launch resulted in not a single instance of the product exceeding its required temperature range during distribution, increasing the delivery yield by five percent.
ISCgold™ and ISCsilver™ Ambient Temperature Profiles

The following shows the new ISC 72-hour profiles. Additional profiles which follow the same basic logic are available from 24 to 144 hours.

1. Temperature is idle at warehouse temperature for several hours prior to pickup.
2. Temperature gradually increases / decreases towards extreme during ground pickup. Gradual ramps are used rather than immediate temperature changes.
3. Extreme temperature occurs during ground transit and loading into aircraft. (Hot extremes and cold extremes occur at different times during the day so the spikes do not line up.)
4. Moderate temperatures occur during air transit and idle time while package is sitting at 3PL warehouse.
5. Extreme temperature occurs again during ground transit prior to package delivery.
6. 24-hour cycle repeats itself to represent both day/night cycles as well as potential secondary transit step.
The diagrams below compare the 72 hour, ISCgold™ and ISCsilver™ Ambient Temperature Profiles with ISTA 7D and 7E ambient profiles.

### Summer Ambient Profile

- ISCgold
- ISCsilver
- ISTA 7D
- ISTA 7E
- ISTA 7E Severe

### Winter Ambient Profile

- ISCgold
- ISCsilver
- ISTA 7D
- ISTA 7E
- ISTA 7E Severe
The diagrams below are comparative examples of the 72 hour, ISCgold™ and ISCsilver™ Ambient Temperature Profiles along with two known challenging industry profiles.
**COMPARISON ANALYSIS METHODS AND RATIONALE:**

Since the temperature curves formed by the ambient profiles often intersect one another, no single analysis method can definitively conclude which one of the many profiles to be the worst case. For this reason, a series of methods are used to analyze the ambient profiles, which include average temperature, mean kinetic temperature (MKT), area under the curve, and thermal modeling analysis.

**ANALYSIS EXECUTION:**

All analysis methods listed above are calculated using Microsoft Excel. The thermal modeling analysis was calculated using ThermoSafe Brands’ proprietary Temperature Prediction Model (TPM) programmed with a theoretical shipper. Results are populated into a table with the following headings for the columns:

- Profile Description
- Duration
- Thermal Modeling Results - Low and High
- Mean Kinetic Temperature
- Average Profile Temperature
- Area Under the Curve

**DEFINITIONS:**

**Average temperature**

The average temperature is the arithmetic mean temperature of all data points within a single ambient temperature profile.

**Benefits:** The calculation of average temperature is valuable because it provides an overall number that relates to the temperature exposure.

**Limitations:** Arithmetic mean is not indicative of extreme fluctuations in temperature as can be experienced within product transport and distribution.

**Area under the curve**

The calculation for area under the curve incorporates the length of the profile into the comparison. This value is calculated by taking each temperature point's difference from 5°C, (the center of the 2°C to 8°C range) and then adding all of the differences, essentially multiplying degrees (°C) by time (hours).

**Benefits:** The area under the curve provides a generic representation of potential heat transfer into the package. Calculation of actual heat transfer would be dependant on other specific variables, such as surface area, insulation type/thickness, and temperature difference across the thermal resistance, etc. which are not mandatory for basic ambient temperature profile comparison.

This calculation will predict a challenging profile of elevated temperatures with a higher degree of accuracy than looking at only the average temperature or MKT because it totals potential heat transfer over time.

**Limitations:** The element of duration in the calculation of area under the curve is misleading when determining a challenging cold profile. This is due to the fact that longer durations will continue to add to the area under the curve even if temperatures are relatively cool. This can cause a colder ambient to appear warmer strictly because of duration.
Mean Kinetic Temperature (MKT)

MKT is different than a simple average. It is defined as “a single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The MKT is higher than the arithmetic mean temperature and takes into account the Arrhenius equation” (International Conference on Harmonization ICH Q1A).

Benefits: MKT and simple averages are good methods for determining a single value where the highest and lowest values represent worst case.

Limitations: These methods are not sensitive enough to capture when an extreme profile will cause a package to exceed temperature criteria, due to a heat/cold spike when this spike is balanced by extreme temperatures in the opposite direction or by long durations at milder temperatures. Although MKT is generally more applicable to long term storage, its value is an effective way to capture the greater impact that temperature extremes pose as compared to a simple arithmetic mean analysis which tends to filter the impact of extremes. These calculations also do not account for profile duration. Duration can have a significant impact on relevancy of average temperature and MKT in that longer durations at mild temperatures can potentially cause greater total heat transfer on the system than shorter durations at warmer temperatures. While MKT should not be used as a sole means to analyze a profile, it can be used effectively in combination with other methods to provide a more comprehensive and accurate profile.

The Right Container Saves Money, Maintains Product Quality

All containers are not created equal. Some suppliers create boxes that are designed to maintain their contents between 2-8ºC, but the Ambient Temperature Profile that the box was designed to may not represent the extreme temperatures that the product experiences in actual use. For example, if a customer ships a product to far-northern destinations in February, the temperature that this product experiences may be lower than the temperatures reflected in the Ambient Temperature Profile that was used to originally qualify the shipper. Consequently, that product could very well freeze during shipment, requiring a replacement (increasing cost to the manufacturer), or reducing product efficacy (reducing quality to the customer).

Thermal Modeling

Thermal Modeling is an intricate mathematical engineering analysis that predicts the thermal performance of a package based on fundamental heat transfer equations. This analysis can be used to predict how a package would perform against selected ambient temperature profiles.

Benefits: Thermal modeling provides a three dimensional analysis containing the interaction of all the elements within the packaging system at any and all points along the simulation timeline. This elevation in temperature is localized to one segment of an ambient temperature profile. One aspect of an ambient temperature profile that no single value calculation can accurately convey, but thermal modeling can, are the times at which extreme temperatures are experienced.
These results demonstrate that by comparison, the ISCgold™ Ambient Temperature Profile is the most extreme winter profile. ISCgold™ is definitively shown to be the most extreme summer profile since it has the highest values for all four analysis methods.

Furthermore, by comparing ISCsilver™ to the standard ITSA 7E profiles, it can also be demonstrated that these profiles are generally within 5% of one another.

**Limitations:** Thermal modeling is theoretical. Actual results are based on a sample package which may not be representative of every shipping package application.

The application of multiple analysis methods used in the development of the ISC Ambient Temperature Profiles provides the most comprehensive and accurate result.
CONCLUSIONS:

- No reliable industry standard ambient temperature profile currently exists for the design and development of insulated packaging systems used for the transport and distribution of drug products.
- Global regulatory authorities are placing increased scrutiny on documenting control over distribution environments.
- Current methods for determining ambient temperature profiles lack consistency.
- Many organizations lack the resources or experience to accurately assess the applicability of ambient temperature profiles used in package design.
- Analysis incorporating average temperatures, MKT, area under the curve, and thermal modeling is a comprehensive and scientifically sound rationale for comparing profiles and for determining the applicability of ambient temperature profiles for the design of insulated packages used to protect temperature-sensitive drug products.

SUMMARY:

By developing two reliable and statistically relevant ambient temperature profiles, ISCgold™ and ISCsilver™ and incorporating a method to compare profiles, ThermoSafe Brands can now evaluate thermal shipping systems to consistent standards.

By reviewing the customer’s profile, collected data, and shipping lanes, the proper profile can be chosen with consideration given to the risk involved. If a customer has an established lane profile, ThermoSafe Brands can compare it to our line of standard products and match the proper product designed to the proper ambient temperature profile.

This will be of great benefit for the packaging design needs of drug product shipments that are required to maintain strict temperature range during shipment and storage. This methodology will also enable shippers to simplify their packaging needs, ultimately reducing shipping material inventory, saving space, time, and money.
ABOUT OUR COMPANY

ThermoSafe Brands is the leading global provider of temperature assurance solutions and the largest manufacturer of packaging components and provider of thermal engineering & testing services for the life sciences industries. With presence in North America, Europe, and Asia, we serve our customers from 11 different manufacturing facilities around the world.

Industry Leading Expertise, Personal Service

An industry leader in cold chain technology, ThermoSafe Brands has over 22 years of expertise designing complete temperature assurance packaging solutions. Our team is dedicated to working with our customers one-on-one to determine the best possible solution for shipping your temperature sensitive products.

The ISC Labs® Difference

Founded in 1989, ISC Labs is a specialized service focused on thermal package design, engineering, and testing temperature assurance solutions. Our experienced staff of engineers works with customers throughout all phases of the package development and testing process, addressing each unique combination of problems and strategic opportunities. Utilizing industry standard testing methods, our team develops customized, cost-effective, and practical temperature control solutions that can be easily qualified to meet regulatory compliance standards.

Protecting your products... and the environment too!

Making environmentally conscious decisions is important to us, and to our customers. Like many of you, we’re concerned about waste disposal and its effects on the environment. ThermoSafe Brands aggressively supports efforts to minimize the impact of our business and products on the environment.