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White Paper
January, 2012

Practical Application of ISTA Lane Data to Pharmaceutical Cold Chain Strategies

ABSTRACT

ISTA Lane Data represents the most comprehensive thermal information about small parcel shipping. This large data set can be used to create real world "what if" simulations of the performance of thermal packaging with real instances. This paper presents a new method of evaluating this performance using a simple modeling software tool that is now part of ISTA's package. Lane data can also now be sorted by "zip code to zip code" information that yields parameters that are useful for estimating arrival temperatures in the payload. It is a system for generating Cold Chain Strategies by creating performance expectations for packages and a way to estimate outcomes when shipping from and to specific locations.

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Chairman, ISTA Lane Data Study Committee

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Executive Summary

ISTA Lane data represents the first comprehensive database of ambient temperatures experienced by packages in expedited parcel shipping. The project scope was to develop suitable laboratory testing profiles. The basis for suitability in this case was the execution of a pre-approved collection protocol with a rigorous analysis of the data. The result is confidence-based testing profiles collected from the field that reflect expected extremes in both warm and cold weather.

The large database of individual lane information for seasonal extremes also represents empirical definition of the seasonal extremes of temperature likely to be experienced in shipping to specific locations. They present "boundary conditions" for the overall thermal envelope for cold chain shipping in the studied region.

An effective cold chain strategy requires that information about shipping conditions be matched with the known performance of insulated shipping containers ("ISC's). Prior to this, this "matching" has been hampered by the lack of a systematic and quantitative approach. First, data on lane thermal conditions were spotty. Second, intelligence on lane thermal conditions has been difficult to apply to known performance characteristics of ISC's.

The purpose of this paper is to present a detailed method to leverage the ISTA lane data for specific ISCs over specific shipping lanes.

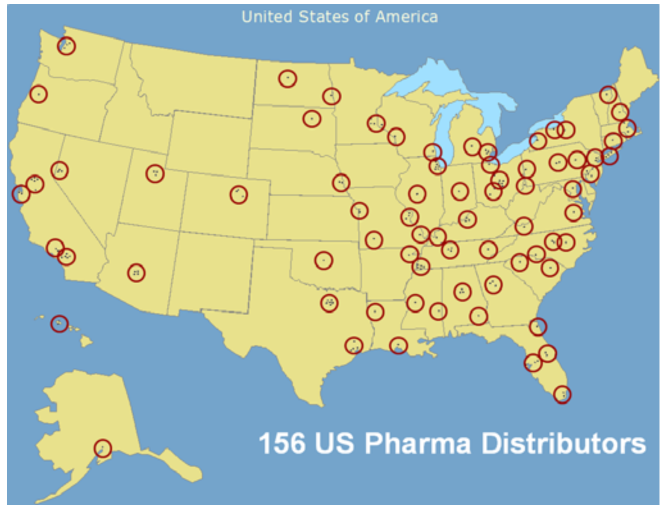
A key element introduced in this paper is called a Slope Response. A Slope Response is the function that defines a relationship between the mean lane temperature and the product temperature within the ISC at specified durations during transit.

Output of the Slope Response function will provide a sensitivity analysis that yields insight into interactions of ISC specifications, the routing, and service level. Every ISC can be characterized by using the ISTA data package with the Slope Response tool.

A software tool that is part of the ISTA Lane data package takes input data in the form of origination and destination zip codes. It uses that input to select the closest geographic equivalent lane data set, and then reports the expected extreme mean temperature for that lane.

This approach to cold chain strategy provides a practical method to field data in making informed choices of packaging and shipping methods to optimize shipping efficiency and to assure safe transit of thermally sensitive materials.

A complete discussion of the use and application of the Slope Response function is contained in the Appendices.



ISTA Lane Data - An Overview

In 2008 and 2009, ISTA sponsored a cooperative project with a consortium of university, supplier, and pharmaceutical manufacturer participants. In the largest study of its type, of ambient temperatures occurring in the small parcel shipping environment was recorded. The technical details of this study, which generated a comprehensive time temperature database of shipping ambient temperature data during seasonal extremes, appears in ISTA Document 0043-RPT and has been explained in numerous public presentations[i].

Rationale for the Lane Data

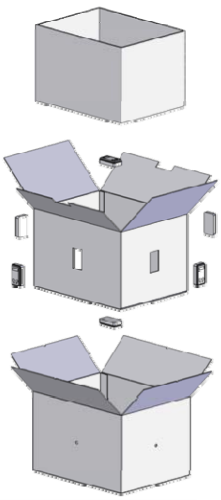
Due to time and resource constraints, pharmaceutical manufacturers have used a limited amount of data collected over a small number of shipping lanes to justify the use of all lanes to all destinations in all seasons. The results of this practice have been mixed. Some packages have been over-designed resulting in complex and expensive solution, while others have been under-designed and the result is product loss.

This ad hoc approach to a cold chain strategy has not been satisfactory for many reasons. Most notably, the wide range of temperature conditions based on seasonal and geographic variables creates a disturbing uncertainty. ISC's that are purpose designed based on limited lane data have unknown applicability in different shipping environments. In fact, the general lack of a standard for comparison of ISC performance has hampered attempts to bring structure and rational procedures to cold chain strategies, in general.

A lack of an appropriate standard for the testing and characterization of ISC's stimulated a panel of experts working with ISTA (International Safe Transport Association) to make a plan to create such a standard. Representatives from the Pharmaceutical Industry, suppliers and other industry experts met in a series of meetings in 2007. Their plan was to identify known shipping destinations where pharmaceutical wholesalers were located. From these wholesaler locations, the nearby parcel service reception points were selected as representative destinations.

Since parcel shipping typically involves shipment from one point through a hub, and then out from that hub to final destinations, it was resolved to measure temperature variations going out from the chosen parcel hub in Louisville, Kentucky and thence returning to that hub. So, for each representative destination, a thermal profile would be obtained O*utbound* and *Inbound*. With these two types of profiles, a complete picture of the small parcel shipping environment would be captured by putting temperature monitors in boxes shipped to and from these representative destinations.

In order to characterize the climatic boundaries of the small parcel shipping environment, the plan called for three replicate *Inbound* and *Outbound* data sets based on successive weeks in the hottest month of Summer and the coldest month of Winter. The goal was to "bracket" the type of exposure that parcels would experience in the most challenging of conditions.



The studies spanned 2008 and 2009. Standardized parcels, known as TASH units, (Temperature Acquisition Shippers) were used as the basis of the study. These were shipped O*utbound* and *Inbound* and then the data from each leg of the journey was gathered and averaged. Several temperature monitors were attached to each TASH to gather external temperatures in the shipping lanes. A total of 83 lanes were used, covering all of North America including Alaska and Hawaii.

From this data, a single average profile was obtained. Although data was gathered more frequently and in different positions on the TASH units, certain mathematical procedures were used to come up with hourly data points representing a profile to be used for the intended standardized profile, the goal of the study.

Each point in the standard profile represents an average that is the result of (a) three time intervals (measurements were taken every 20 minutes), (b) six positions in a TASH container (top - front - back - left side - right side - bottom) and (c) two shipment directions (*Inbound* and O*utbound* from a specific location to and from Louisville, Kentucky).

Shipment elapsed times were corrected for time zone differences and differences in pickup time details based on shipping documents provided by the participating parcel service. In other words, the data were "harmonized" so that they represent a certain point in daily time for origination of a shipment.

Profiles for a Testing Standard

The profiles, known as ISTA 7E lane profiles, consist of one 72 hour Summer profile and one 72 hour Winter profile. For convenience, the profiles are repeated from the 24-hour point to extend the profiles to 144 hours if testing of ISC's require. Data, for the most part, was collected up to the 72-hour point and only beyond in limited cases.

These profiles are intended to represent the average hottest and coldest seasonal conditions within the micro-environment of the small parcel. They are not "climate data sets", but rather a reflection of the conditions in trucks, transit storage facilities and air cargo spaces. They also take into account the consequences of handling. They are not about weather, but rather shipping conditions. These are a "real world" profiles that are believed to be representative of the day-night and latitudinal variations in the shipping environment.

The TASH study is the most comprehensive research performed to date on shipping lane temperature variations. In sum, over 5,000 individual temperature records were studied and analyzed comprising over 800,000 individual time temperature observations.

Usage of Profiles

The profiles are intended to form the basis for a standard of comparison for ISC performance. All ISC's are offered to the industry with testing data. A programmable temperature chamber is typically programmed to create a time vs. temperature profile. This is verified by placing thermal sensors in the air space of the chamber. Thermal performance of the ISC is measured by placing sensors inside of the container as it is being exposed to a profile in the programmed chamber. Since ISC's are provided with insulation materials and phase change materials to maintain temperatures in range during shipment, the performance is measured in terms of the time that the internal temperatures can be maintained for product security and efficacy upon arrival.

As mentioned earlier, prior to the introduction of ISTA 7E, there was no standard for comparing different ISC's. From design to design and manufacturer to manufacturer, it is very difficult to know if the performance of one ISC is better or worse that another for a particular cold chain challenge. Adoption of the 7E profiles as a global standard addresses this issue.

Common Laboratory Deliverables

However, even though having a single global standard for testing ISC's to a standard profile, there are still issues that need to be addressed to achieve the goal of ISC global comparability. Training level of personnel and laboratory competence are issues. Standard formats for reporting, data collection and procedures are extremely important issues. These need to be certified to provide the assurance that ISC selections can be made without lab to lab bias.

So, ISTA has partnered with several industry leaders in the Pharmaceutical industry to bring a companion standard to the performance of actual ISC testing. It is called Standard 20. Standard 20 sets forth in comprehensive documentation exact procedures for actually using the 7E profiles in a test environment where the lab, the personnel and the protocol are certified and consistent. Standard 20 contains full documentation, examples of protocol, qualification and data reports, full instructions and testing and reporting criteria. For years, ISTA has been active in setting testing lab standards for transport packaging. With Standard 20, they have reached a new level by not only setting the standard, but by providing a highly structured context in which to perform testing.

ISTA first provides training for eventual professional qualification of laboratory technicians and technologists. They provide a mechanism to certify laboratories as competent to run 7E profile tests on ISC's. And finally, they have the capability to review the final results of 7E testing performed by ISTA certified personnel working in ISTA certified labs. With this review, an ISC can be issued an ISTA certified "stamp" that attests not only to the tested performance of the ISC, but also to the fact that the testing was done in known and certified conditions.

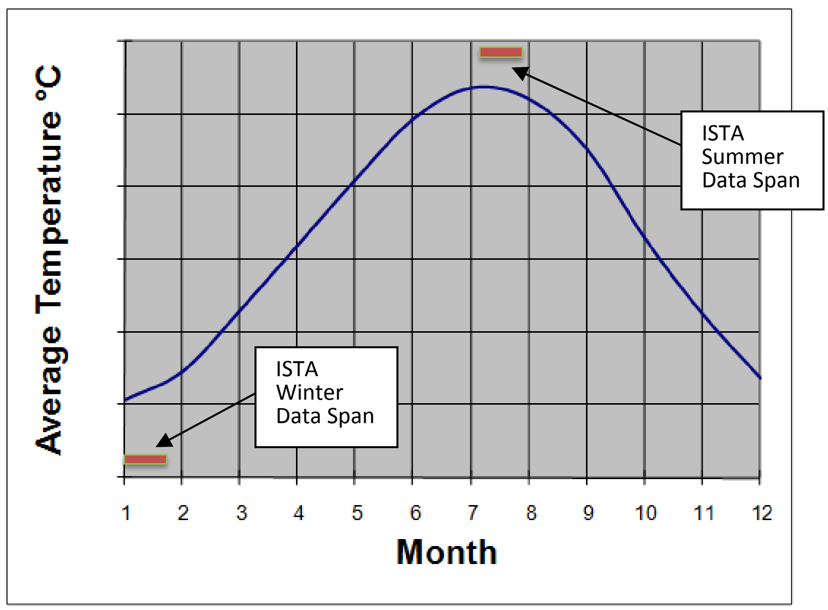
The significance of an ISTA certification of ISC products cannot be overstated. When ISTA certification is in practice, Pharmaceutical companies can then shop for ISC's based on simple and reliable criteria. They can have confidence that performance is not subject to unacceptable uncertainty. ISTA certification opens markets for shipping containers to a wider range of suppliers. Cold chain strategies can be constructed based on known reference numbers for package performance.

The profiles have been viewed in two distinctly different ways. First, the idea is that the profiles will create the basis of for a universal solution for shipping if the profiles are employed as a testing standard. One well known engineer based at a large pharmaceutical company has stated that "over 99% of shipping" done by that company is encompassed safely by the 7E standard. Second, the idea is that the profiles are simply an inter-comparability standard that has its primary utility when comparing the performance of different ISC designs.

Acceptance of either or both of these two different ways of evaluating the lane averages is to be expected. The profiles are not a guarantee for an all lane all weather solution, because there are confidence levels attached to the profiles. When and where these extreme events occur is of interest to the shipper, and the risk based approach can be taken with the data supplied in the ISTA 7e package and the Slope Response tool, which is the purpose of this paper.

Relationship to Climate and Annual Extremes

Annual variations in climate follow predictable patterns. Especially in temperate areas, the pattern resolves to an annual curve that looks like this generalized plot seen at right[ii]. The ISTA lane strategy was undertaken as an effort to "bracket" this annual variation scheme, so that the thermal challenges to shipping could be measured, in a sense, at the extreme peak and valley of this function. According to US climate data, this type of curve applies to all climate regions in the tested area of North America, and due to the generality of this function in a global sense, is broadly applicable.



The bars in January and in July represent the two periods of the ISTA lane study. As is evident, these represent the annual extremes that would be expected in this temperate model for seasonal variation.

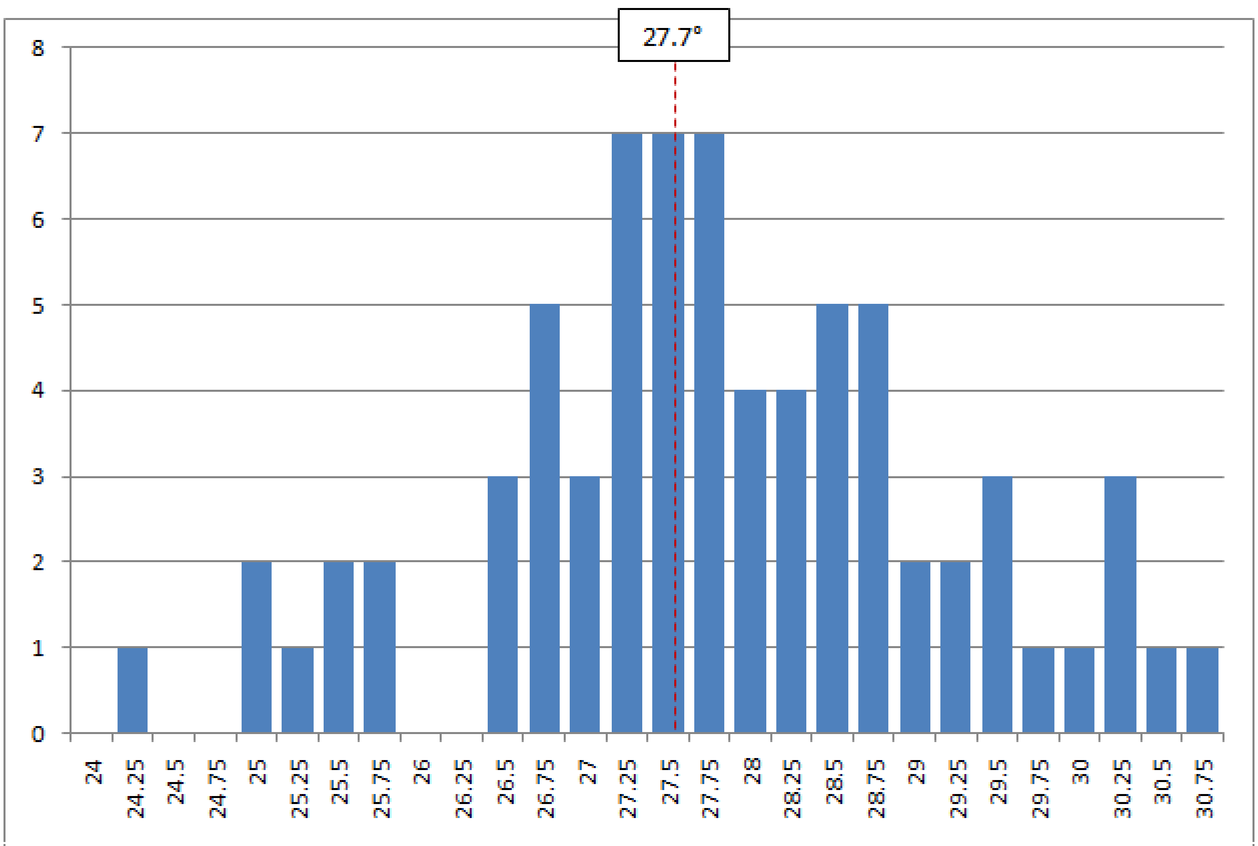
Of course, this graph was derived from a large database of outside temperature values, and one is careful to note that the temperatures are ones observed in the *shipping environment*. The shipping environment is not the same as the "outdoor" environment. The interior of trucks, aircraft and holding warehouses generated the data of the ISTA lane data. Generally, the same trends apply to the shipping environment, but the specifics of temperature apply to a moving environment partially protected from outside "weather". For absolute values, "weather" data are truly not appropriate for judging ambient conditions that insulated packages in shipment may experience.

Exceptional Lanes: Summer Example

So, the data represents knowledge about the types of conditions that may prevail during annual extremes. Since the data were replicated in three separate weekly *Outbound* and *Inbound* monitoring sequences, the data encompasses the variation that may be expected in these extreme parts of the year.

If we accept that the use of the 7E profiles will provide a challenge profile that will result in a "99%" percent confidence interval of safe arrival when applied as a criterion for ISC design, then we can focus on the key question: what about the exceptions? Here is a quick look at the data so that we can define the scope of this question:

Summer lane data shows a wide range of average values. In the histogram below, the distribution of average values shows a range from 24.1°C up to 30.7°C (these are 72 hour averages, corrected for shorter durations by truncation).



The vertical axis is frequency and the horizontal axis is average 72 hour temperature for lanes. The dashed red line represents the average for the 7E profile (a type of "grand mean").

This date shows that the data for the summer (by averages) is pretty much within 3°C of the overall mean. We hear a lot about "spikes" of temperature, and many believe that these are a significant feature of thermal challenge profiles. A wealth of discussion has taken place since this issue was first raised at the USP Packaging and Standards meetings in the 1990's. It seems that there is no broadly accepted definition of a "spike", nor is there any quantitative data that links a definable spike event with that event's impact on internal package temperatures in a cold chain setting.

We would arbitrarily define an excursion lasting over an hour as a spike. We need this to begin to look at the data. It is almost certain (see later sections) that any event of less than this duration is unlikely to have an impact on the internal temperature of an ISC due to the damping factors involved.

Since the generalized range of average temperatures clusters around the mean by about ±3°C, then one could ask: to what extent do we see "spikes" outside of this range during this extreme season? It would seem reasonable to state that lane data sets that have such events are exceptional lanes.

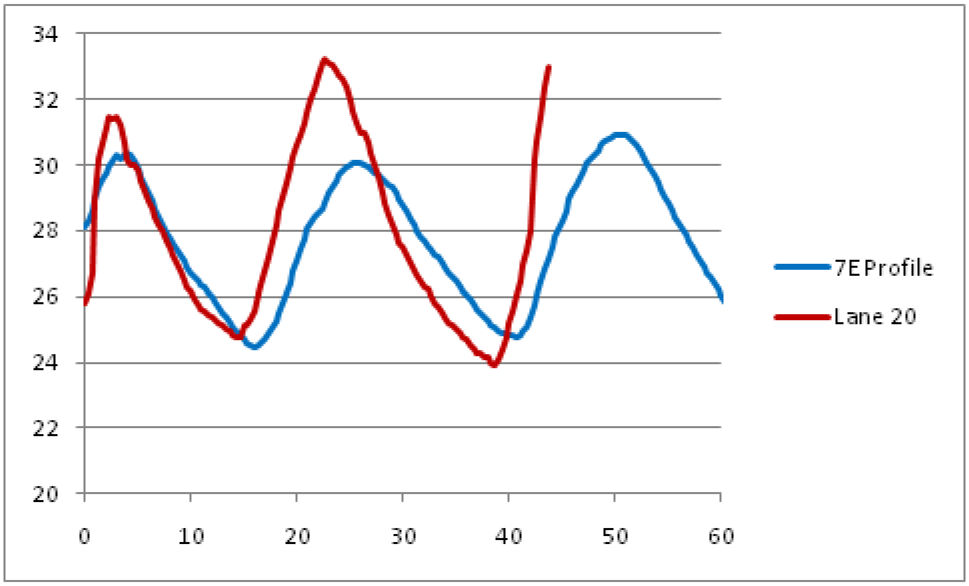
Lane	Average 72 Hour Temperature[iii]	Max Out of Range Value °C	Hours Outside Envelope
1	**24.1**		
78	**24.8**		
6	**24.8**		
44	**25.1**		
51	**25.4**	1.0	1
58	**25.5**		
45	**25.6**		
77	**25.7**		
57	**26.3**	1.9	2
47	**26.4**		
12	**26.4**		
8	**26.5**		
31	**26.6**		
79	**26.6**		
28	**26.7**		
52	**26.7**		
50	**26.8**		
23	**27.0**		
32	**27.1**		
83	**27.1**		
59	**27.1**	1.8	2
55	**27.2**		
80	**27.2**		
60	**27.2**		
11	**27.2**		
63	**27.3**		
10	**27.3**		
9	**27.3**		
27	**27.3**		
3	**27.4**		
33	**27.4**	0.6	2
46	**27.4**		
21	**27.5**		
84	**27.6**		
54	**27.6**		
40	**27.6**		

43	**27.7**		
75	**27.7**		
39	**27.7**		
7	**27.8**	1.0	2
61	**27.8**		
64	**27.8**		
25	**27.8**		
20	**28.0**	2.0	7
76	**28.0**		
30	**28.0**		
68	**28.2**		
34	**28.2**		
22	**28.3**		
48	**28.3**		
4	**28.4**	0.9	2
65	**28.4**	0.0	
2	**28.4**	0.2	
56	**28.6**	0.3	
19	**28.6**		
24	**28.6**	1.0	1
41	**28.7**		
74	**28.7**	0.7	1
14	**28.8**		
26	**28.9**		
16	**29.1**		
42	**29.2**		
15	**29.3**		
69	**29.3**		
35	**29.5**	1.4	4
36	**29.6**	1.2	1
17	**29.8**		
37	**30.1**	3.3	6
49	**30.1**	4.0	17
72	**30.2**	0.5	1
71	**30.4**	2.7	4
73	**30.7**	2.0	3

If the lanes for which sufficient data are available are studied for this exception criterion, some of the lanes have one or more temperature events that fall outside of the envelope.

Notably, there is one lane (20) that has an average value just above the 7E profile average, but nonetheless shows 7 hours outside the ±3.0°C envelope. (See graph on next page).

Almost all of the summer lanes shown here, with few exceptions, cluster tightly around the mean expectation of the ISTA mean profile. One aspect of these data is that--despite the occasional spike activity--the impact of these ambient temperatures is more related to the means that the maxima and minima observed in the profiles. This is discussed in some detail later in this document.



One might reasonably conclude that Lane 20 would be best assigned to the "exceptional" category.

Examination of other "low average but with at least 1 hour out of range" instances do not seem to warrant exception.

So, if we designate the criterion "at least two hours out of tolerance range" and above the 7E average, then there are 7 "exceptional profiles", or approximately 10% of all profiles with sufficient data for analysis.

If we choose a more stringent criterion, say "more than two hours out of range" then the number diminishes to 5 profiles, or approximately 7%.

For purposes of a reasoned argument, it is perhaps safe to say that 10% of lanes show temperature ranges that have spike signatures and averages that justify calling them "exceptional lanes".

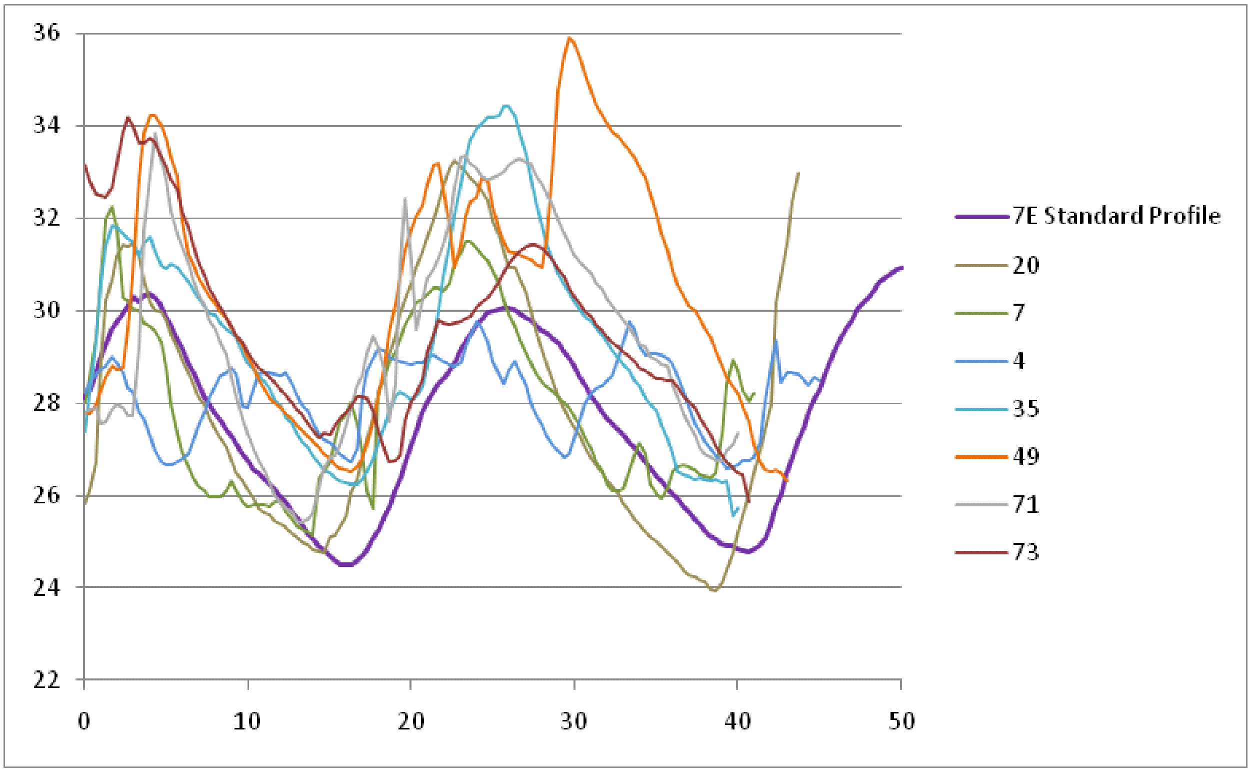
To get a generalized feel for the significance of these exceptional lanes, consider that they are confined to about 10% of the year (based on 6 weeks of extreme hot or cold conditions in a 52 week year), and that approximately 10% of lanes seem to exhibit significant excursions. That is about 1% of all annual shipping. This conforms to the offhand remark we quoted earlier.

This type of math is not intended as the basis for a suggested cold chain strategy, and one must warn that it is for the purpose of illustration. It gives an idea of the relative extent of times and places where extreme thermal conditions in the shipping environment are likely to occur.

Note that this analysis is for summer conditions. An analysis of winter conditions shows that the challenges are perhaps more challenging that the Summer ones. We address this issue at length in a later section.

Perhaps the most significant aspect of the lane variation is the relative absence of pronounced spikes or valleys. The data variation is most accurately characterized as a typical oscillation (as reflected in the 7E mean profile), but with upward or downward shifts from that mean expectation.

Looking at the most extreme lanes identified above, it is clear that these are primarily an "upward shift" of the pattern shown in the 7E standard profile.



The preponderance of lanes has the same profile characteristics, but is much closer to the mean profile.

The winter data shows a similar pattern, but as the histogram plot (see page 18) reveals, the low temperature exceptions range much more away from the central cluster of lane averages.

Despite all of this, one does not really know in a quantitative sense how significant *variations* in temperature are as opposed to overall thermal impact (*average temperature*). While the whole issue of excursions and exceptional lanes seems to offer a way of understanding the thermal challenges one might expect in extreme situations, there is no way to assess the impact of these challenges without knowing about ISC responses to variations and to averages.

The focus of the upcoming sections in this document is how to actually do such an assessment. When that becomes possible, the lane data take on a new significance in terms of how they can be used to shape a cold chain strategy.

The Value of Lane Data: Cold Chain Strategies

Knowing how extreme thermal conditions can become in your cold chain (in terms of time and place) can be of extraordinary value. The biggest challenge is not in knowing of such conditions as data sets, but the *application of that knowledge to prediction of outcomes*.

Prediction must depend upon

- selecting the correct data set for a particular shipping instance and then
- applying some intelligence of what that data set means for the type of shipping container that will be used in that shipping instance

If this is done correctly, there is a powerful case that one has done everything that could possibly be done to assure a safe arrival of a product.

Geographical Aspects and the Concept of Shipping Zones

Generally, when a package enters the shipping regime in a distribution operation, the "known" data on its regional destination is the zip code. All distribution schemes, worldwide, depend upon the same type of regional designation by a code. So, when shaping a cold chain strategy, one of the key variables is related to this type of coding.

Zip Code Databases

Zip codes represent a defined regional zone with a "centroid" that is characteristic of that regional area. The centroid is the geographic point that is exactly in the middle of that area. This data is available in numerous commercial databases. So, if you know a destination in terms of its zip code, you can determine the most proximal, or nearest zip code by applying this database information. In this way, a limited number of zip codes can be related, by nearness, to the entire list of zip codes that exist.

One can ask the question: "I am shipping from zip code XXXXX and my destination is zip code YYYYY. What lanes in the ISTA lane database are closest to the lane defined by these zip codes? This becomes an important question in relating lane data to a specific shipping instance, and can be answered by ISTA data relevant to the question.

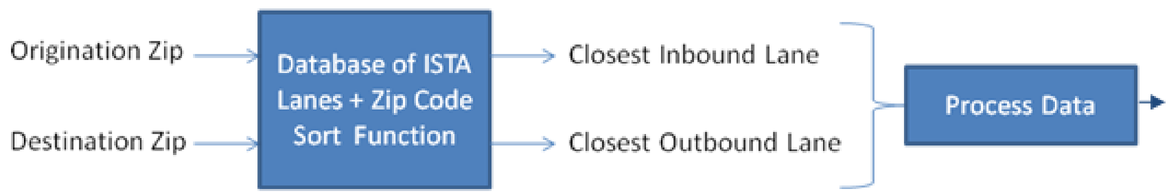
Relating a Zip Code to a Shipping Instance

All of the ISTA lane data is comprised of trips from Louisville, Kentucky (a major distribution hub for small parcel distribution) and destinations that were deliberately selected to represent a cross section of typical arrival destinations. Each of these destinations can be designated by their unique zip code.

Each of the lanes represents an *Outbound* trip to the specific destination or an *Inbound* trip from that location back to Louisville, Kentucky. So, if I know that I am shipping from XXXXX zip code to YYYYY zip code, then I can tell which pair of *Inbound* and O*utbound* lanes in the ISTA lane data set is most closely related to that shipping instance.

When I know the identity of these 'most-geographically-similar' lanes, then I can deduce the thermal conditions that might closely apply to my specific shipping instance. This means that the ISTA lane data can be used in a way that tells us something about expected thermal challenges in the most extreme cold and hot seasons, for that shipping instance. That is potentially a useful way to apply lane data intelligence.

A more general approach is to cluster like thermal profiles and then relate a specific shipping instance to a series of thermal zones that have a quantitative relationship to the lane data and the zip codes involved. The paradigm can be understood as follows:



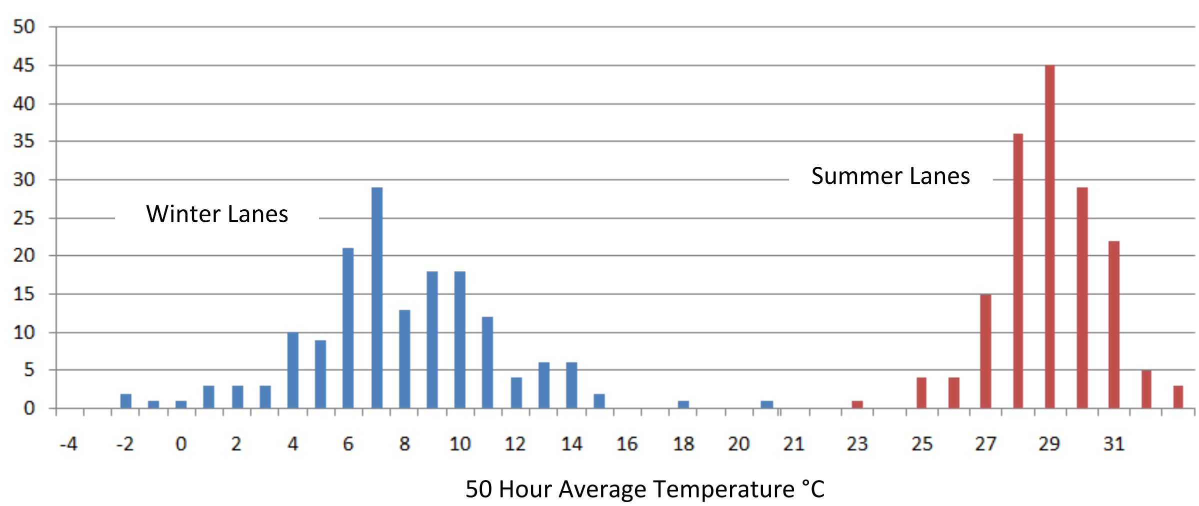
The processed data could consist of a "synthesized" profile that is specific to the shipping instance or the designation of a mean temperature that characterizes that instance[iv]. We present data and analysis below that adds credence to the notion of this approach.

We have analyzed the lane data with this approach in mind.

Using full duration lane averages, one can see the large thermal variation that is related to lanes:

	Summer *Inbound*	Summer *Outbound*	Winter *Inbound*	Winter *Outbound*
Max	31.1°C	31.0°C	20.2°C	17.9°C
Min	23.4°C	21.8°C	-2.5°C	0.7°C

These data represent a 9.3°C span in summer and a 22.7°C span in winter. This asymmetry suggests a different approach to "thermal zones' for each. There are countless ways to group lanes by these thermal data, but if we use frequency distributions, it makes the picture a bit easier:



As we will see from the analysis in subsequent sections, the Winter Lanes in the "low tail end" of the distribution will affect the performance of Insulated Shipping Containers in a non-linear way when temperatures drop below certain limits.

Because of this non-linearity, we strongly suggest that the use of lane data be employed as a filter to determine cold chain strategies in a way that puts extreme lanes in a separate category. The following section shows how the physics of thermal transfer in typical Insulated Shipping Containers and how these containers might be expected to respond specifically to the lane conditions that were observed in the ISTA lane study.

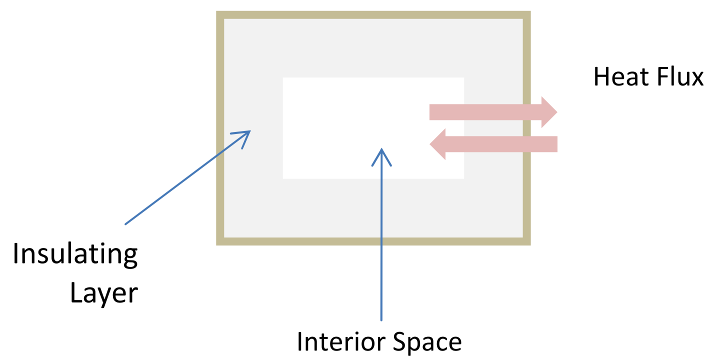
How Do Temperature Profiles Determine Package Conditions? Bridging the Gap between Ambient Data and Internal Temperatures

Lane data is the key to understanding package interior conditions during exposure to differing ambient thermal conditions. Whether one understands this process as a computer exercise or by the application of tacit--or less structured--knowledge, the process is always a form of modeling.

So what is the basis for modeling ISC responses to external temperature conditions?

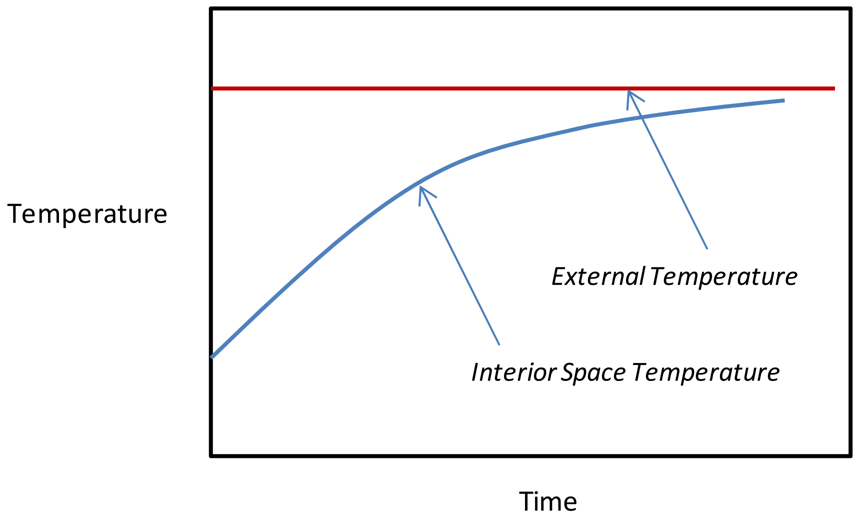
Some Generalizations

The basic physics of thermal transfer in an insulated shipping container is the flow of heat from a warm zone to a cold zone.



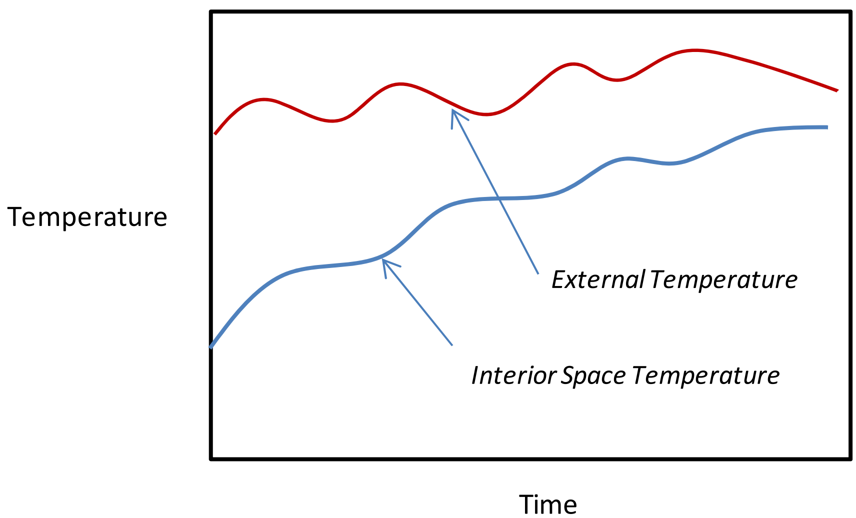
If the interior space has a temperature higher than the exterior air temperature, heat passes out of the container. If the interior space has a temperature lower than the exterior heat passes into the interior from the outside. The Insulating Layer moderates the rate at which this happens. More insulation equals a lower rate of heat flux. Insulation simply works to slow heat exchange processes to keep interior temperature from changing too fast.

One may expect a simple quantitative relationship:



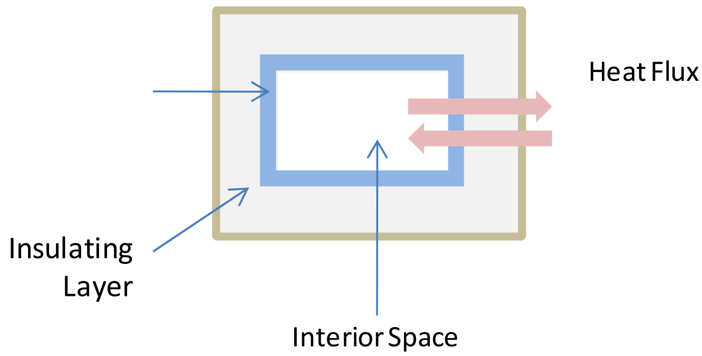
As time progresses, the internal temperature becomes asymptotically closer to the external temperature.

If the external temperatures fluctuate, the $\triangle$T value fluctuates as a consequence, producing the same general pattern but with some reflection of external temperature changes.

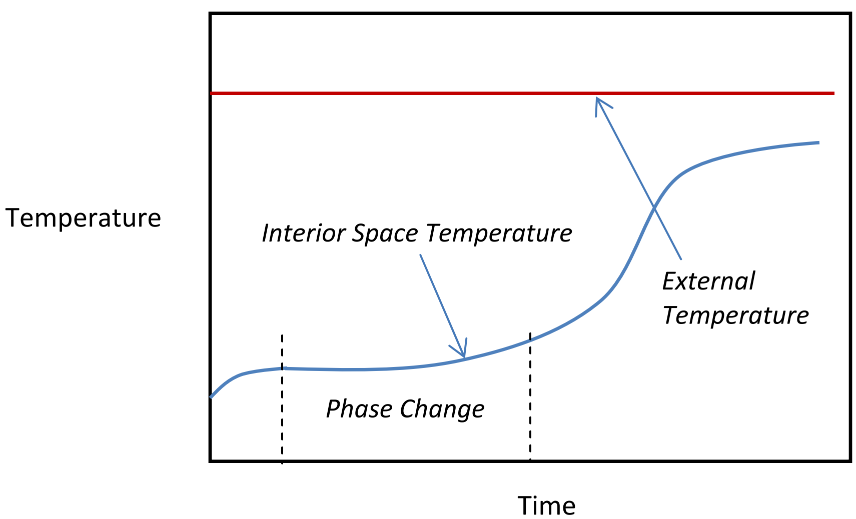


The thicker the insulation, generally, the less impact exterior oscillations will have on the profile of the Interior Space Temperature. In a very well insulated container, the interior temperature profile would look much more like the first graph.

Since the goal is to slow down the processes of thermal exchange, a typically employed technique is the inclusion of phase change material to the container.



Everyone knows about phase change materials. Ice is a good example. Any solid to liquid phase transformation is accompanied by absorption of heat that does not result in a change in temperature of the material. This heat absorption capacity of a melting solid is known as the *latent heat of fusion*. By changing the chemistry of the material, it is possible to manipulate the amount of heat absorbed (per unit of weight of the material) and the melting point. Adjustment of these parameters allows the function of warming or cooling of the interior space to be slowed down during the time course of temperature change. The same heat flux occurs, but the temperature is stabilized due to the effect of the phase change material.



There is an initial rise in temperature as the phase change material approaches its melting point. As it melts, temperature is stabilized; the incoming heat is absorbed by the material without a change in temperature.

Quite a number of quantitative models have been built over the course of several years that take into consideration these physical processes. Each model must be verified by comparing predicted results with results measured in test chambers. Models, in general, have a good predictive record in this regard.

Our purpose is not to propose any specific model, or to discuss the relative merits of different modeling approaches. Any model that emulates actual chamber results and conforms to the general principles discussed here will suffice for the point we wish to make. Our intent is to show how the combination of modeling and a large amount of lane data (like the ISTA lane data) can serve to bring decision making intelligence to the shaping of a cold chain strategy.

Using Modeling in Combination with Lane Data

We used a proprietary model that produces good correspondence with chamber results. The model also allows for the setting of certain parameters for the simulated ISC:

- Product Start Temperature (°C)
- Payload Weight (kg)
- Product Space Area (m^2)
- Categories of Insulation Material (4 different types: high density EPS, low density EPS, polyurethane, and "custom")
- Average Thickness (cm)
- Weight of Phase Change Material (kg)
- Phase Change Material Start Temperature (°C)

Numeric values for these parameters are inputted. Then the model is fed a specific ambient thermal profile. The model then produces a simulated time vs. temperature result for the interior ("payload") space of the ISC.

Two example configurations of ISC shippers were used in an illustrative run of the model in combination with the ISTA lane data. Here are the parameters of the two hypothetical ISC cases[v]:

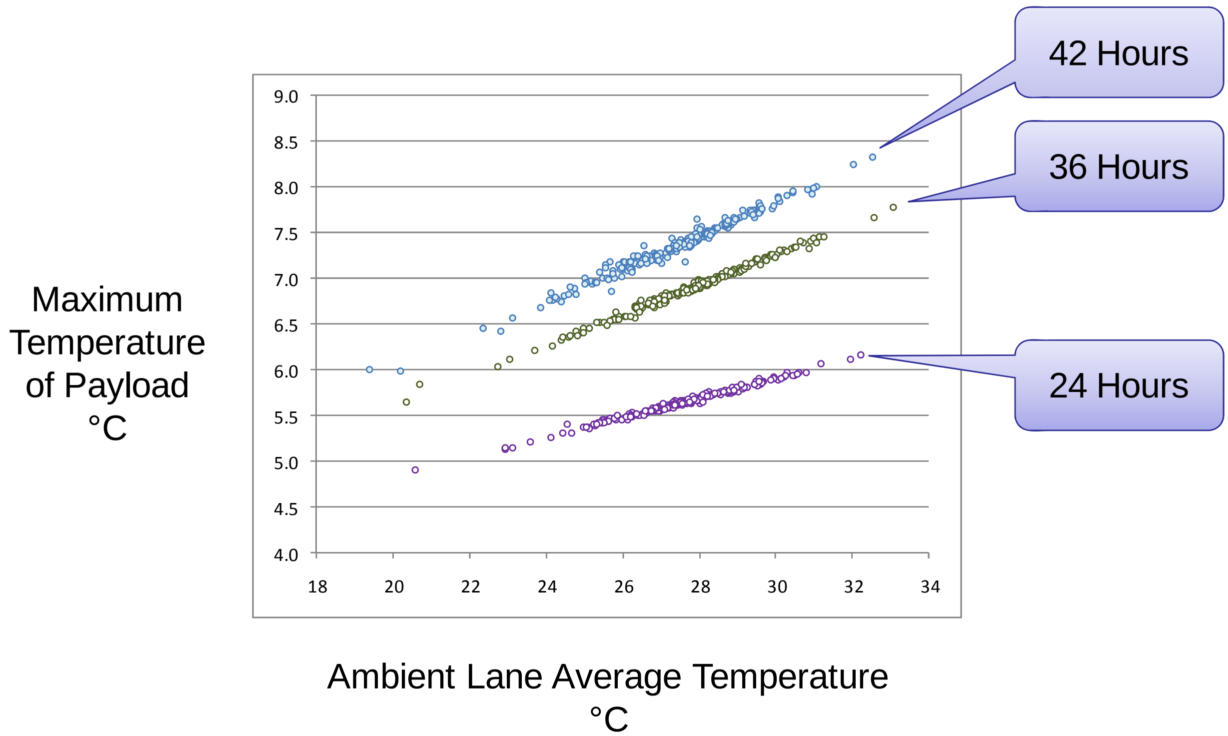
Parameters	Shipper #1	Shipper #2
Initial Product Start Temperature (°C)	5°C	5°C
Payload Weight (kg)	2	2
Product Space Area (m^2)	0.14	0.14
Insulation Material	Polyurethane	EPS
Insulation Thickness (cm)	4	3
Phase Change Material Weight (kg)	2	2
Initial Phase Change Material Temperature (°C)	-5°C	-5°C

Both of these shippers are identical except for insulation type and thickness. The above table summarizes the ISC parameters with emphasis shown for the parameters that were different for the two shipper types.

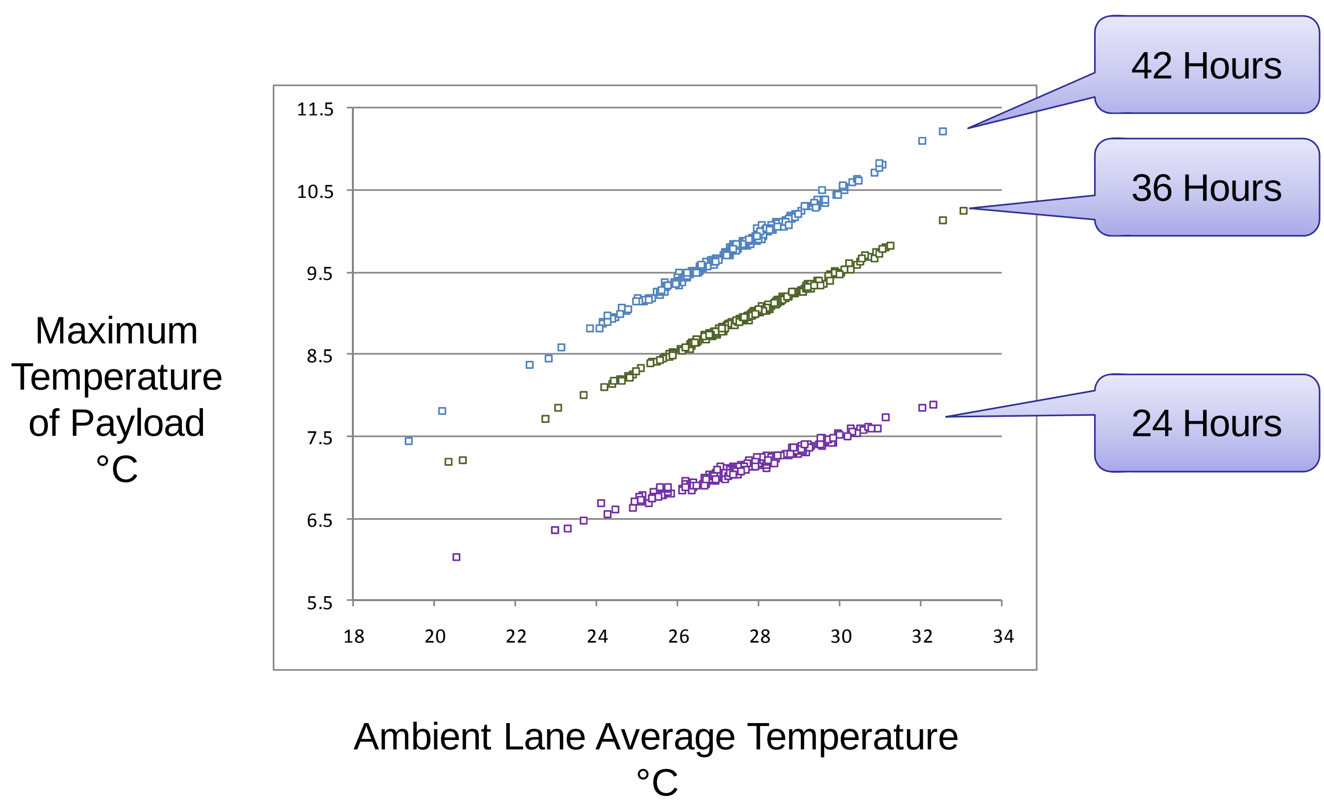
The model was run for each of these shippers for every available lane data set. The model run duration was 50 hours (lanes with at least 50 hours of time-temperature data were used) . The results were analyzed according to time estimate of internal (product) temperatures at different standard times (42, 36 and 24 hours). These temperatures were equivalent to the maximum at the time periods indicated (Summer) and the minimum at the time periods indicated (Winter).

Winter data, summer data and data for each shipper were produced and the results were plotted against the mean temperature (numeric average of the ambient temperatures, point by point, for the specific duration of the tests[vi]).

Shipper #1 All Summer Lane Data



Shipper #2 Summer Lane Data

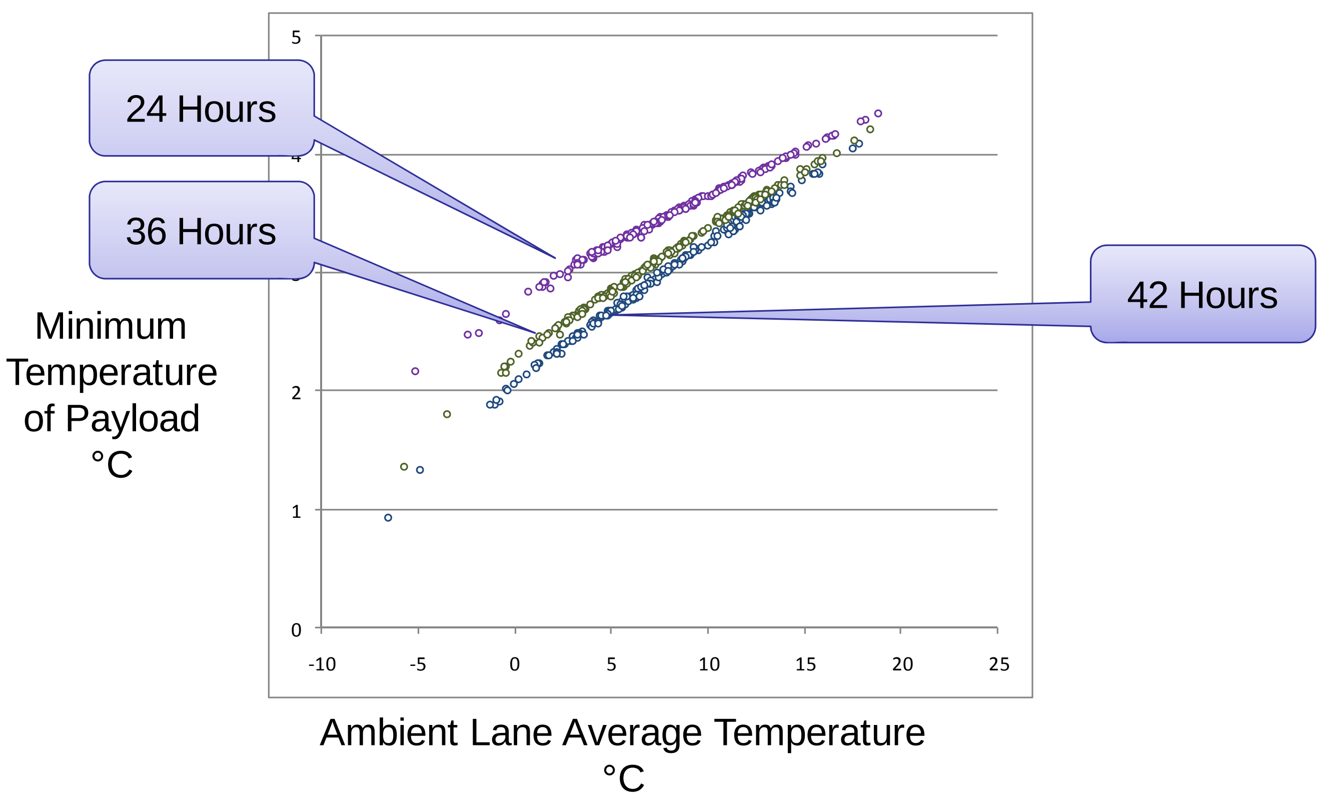


Several observations can be made regarding these results:

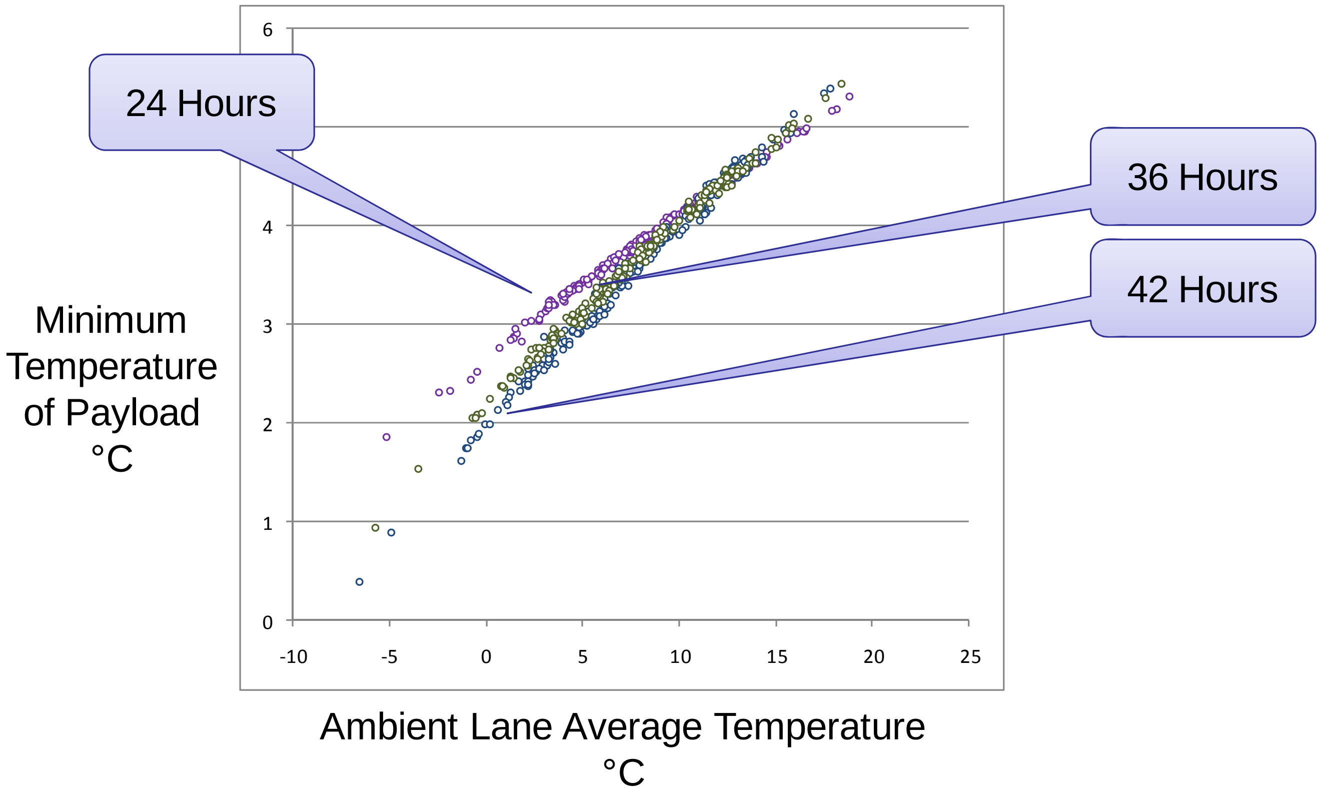
1. A high level of consistency in the correlation between Ambient Lane Average Temperature and the product temperature outcome at the different standard durations.
2. Differences in the applicability of the two different shipper types is profoundly evident: For example...Shipper #1 would be a good choice for a 42 hour duration shipment intended to keep the internal temperature at 8°C or below, Shipper #2 would not at all. Other comparisons are also clear.
3. The slope of the lines is consistent in terms of its pattern within each type, suggesting that this slope would be a good base parameter for knowledge about the performance characteristics of a specific type of shipper.
4. This method of data visualization allows consideration of shipping method as part of a consideration of the performance criterion (internal temperature at delivery), shipper type and expected duration of shipment.

The same type of result is yielded with Winter model runs (same model, same ISC parameters, but using Winter lane data).

<u>Shipper #1 Winter Lane Data</u>



Shipper #2 Winter Lane Data



Similar conclusions to the summer data can be drawn. Although the plots for Shipper #1 and Shipper#2 are more tightly clustered, clearly these shippers would have a greater challenge in the cold seasonal extremes, with a 24 hour shipping regime and Shipper #1 being the only instance that might be trusted to keep the contents above 2°C.

Adjustment of Model Input Values

Adjustment of model input values does not change the relative scatter of the points in any significant way, but changes to payload weight, payload space internal area, weight of phase change material and insulation type and thickness all affect the relative position and (to a lesser extent) the slope of the lines. As the lines trend down in the Summer plots and up in the Winter plots with changes to the model input parameters, one can--in effect--produce an ISC design that is fitted to the performance needs of a shipping challenge that encompasses all of the ISTA lane data.

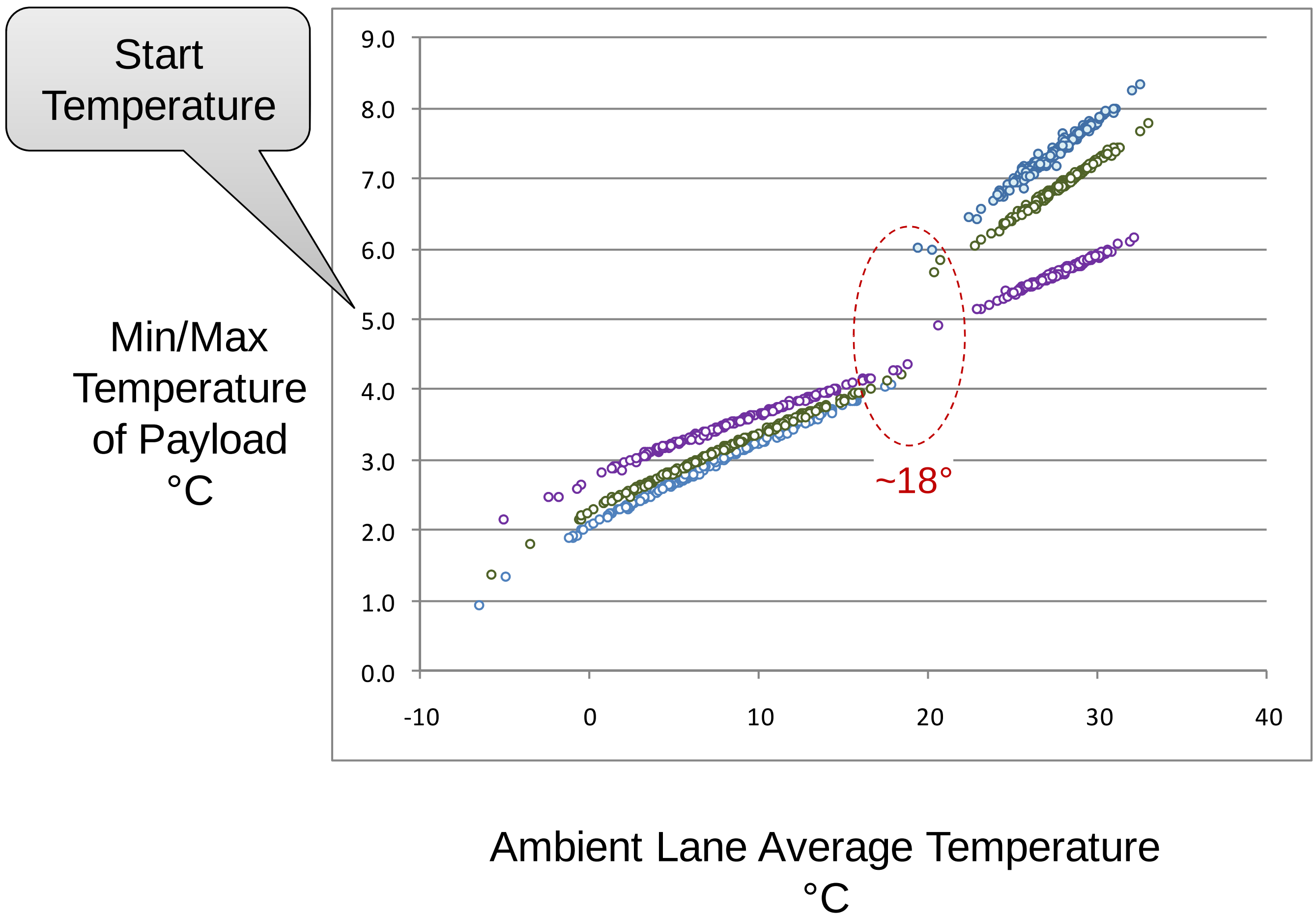
This approach to cold chain strategy is one that has been done in a non-systematic way for years. The difference with the suggested approach, however, represents a comprehensive and quantitative calculation that combines knowledge of lane conditions (including Winter and Summer extremes) and aspects of ISC design to predict outcomes. This is quite different from traditional methods.

We have labeled this new method the "Response Slope" method. It uses a combination of a large database of lane data combined with modeling of ISC responses to each of the lane profiles in the lane data collection.

"Response Slope" as a Universal Parameter for ISC Performance

If we combine the summer and winter data, a pattern of ISC performance emerges.

Winter and Summer Lane Data Shipper #1

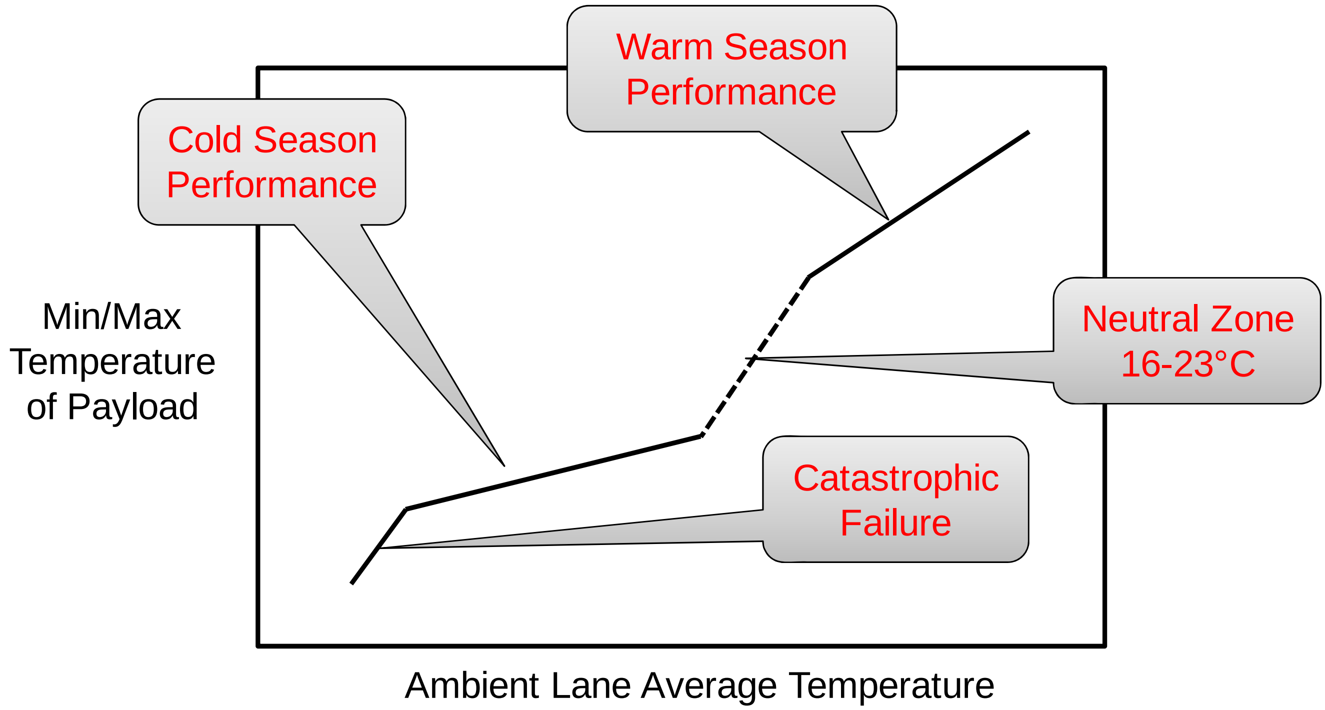


Shipper #1 in this example is typical of many different plots of this kind. In this charted data set, Shipper #1 can be viewed as a comprehensive chart of performance for a universally capable pack out, as compared with a seasonal pack out . The conditions remain the same, and the different slopes remain the same (Purple dots = 24 hours, Green dots = 36 hours and Blue dots = 42 hours) in terms of internal temperature outcomes.

Shipper #1, when used under more benign thermal conditions during the "mid months" between Summer and Winter will quite apparently perform well, in terms of keeping product at the desired temperature. Many scientists and engineers dealing with ISC design and cold chain issues have noticed this neutral zone. The response characteristics are different, but consistent at the extremes of these functions. That is the key point: for any duration of shipping, one can use this approach to create useful information for a cold chain strategy. There is a useful generality to the concepts of this approach.

Notable is the tailing off of performance at the lower end. This suggests that performance more rapidly drops off as extreme low temperatures are approached.

We may consider that a generalized profile may be expected for a wide range of ISC types:



One would wish to know the slope values for Winter and Summer and to be able to specify the types of testing and analysis that would be required to produce these slope values .

At the lowest reaches of the Cold Season Performance Curve, there is a departure of the most extreme examples of lane data from the function. This region, labeled "Catastrophic Failure" above is most likely the result of certain difference of the physics of interaction of an ISC to environmental temperatures during Winter when there is a universal packout (containing a phase change material that starts at a sub-freezing temperature.

Catastrophic Failure in Cold Season Performance

As long as external temperatures are higher than internal temperatures, the net heat flux is inward. This tends to overcome the tendency for the internal temperatures to drop in response to a significant mass of sub-freezing phase change material on the interior of the package. Certain lanes show an average temperature that is lower than the mean temperature of the interior of the package, so in this instance, net heat flux is outward. If this effect is combined with the tendency of winter lane profiles to show a continual decline of temperature with time and the more pronounced "negative spikes" that are characteristic of winter lane profiles.

We can therefore make a considered judgment that this area in the generalized curves above are a conditions where the average winter lane temperature is below the mean internal temperature of the payload and the phase change material combined.

Conclusions

1) Lane spikes are present, but their impact on internal conditions in ISCs may not be as impactful because of the brief durations in the parcel environment.

2) Lane data, summer and winter, represent a lot of information, but the key information for translating this information into effective cold chain strategy is related to how ambient conditions drive the types of outcomes when packages are shipped.

3) The lane data when coupled with a simple model of ISC performance shows repeatable and consistent patterns in the relationship between mean ambient temperature and internal temperature at destination elapsed times.

4) Summer data show that outcomes at fixed hour durations produce clear relationships between lane ambient temperature means and the internal payload temperatures.

5) Similarly, winter data show the same patterns, but with a disintegration of predictability when mean ambient temperatures fall below the average internal temperature of phase change material and product as an averaged mass.

6) Below these limits, a condition of "Catastrophic Failure" seems to occur, suggesting that extreme lane strategy if most appropriately applied to winter conditions.

7) Modeling shows that differences even small differences in ISC specifications have a far more impact on "thermal outcomes" than does the specifics of profile spikes and valleys.

Appendix A - Slope Response Tools Supplied with the ISTA Lane Data Package

ISTA supplies the data in unprocessed form in Excel Spreadsheets. Users may choose to tap into that data for their own data analysis. Information from the spreadsheets is incorporated into two software tools[vii] that purchasers of the ISTA Lane Data Package might find useful. Briefly, these are:

I. ISTA Zip Code / Lane Database - this is an modified Excel workbook with incorporated macros that allow users to input any US Postal Zip Codes and get a return match of lanes that most closely correspond to the inputted codes. Also produced upon input are mean temperatures for different durations corresponding to these "closest lanes". The program compensates in a logic way for the small amount of data gaps that are present in the database of lane data, and uses comprehensive information on each zip code centroid used in the generation of outputs.

II. ISTA ISC Model - this is a modified Excel workbook that accepts ambient lane shipping data in hourly format. When this data is inputted, the model permits the user to manipulate ISC parameters:
   - Product Start Temperature (°C)
   - Payload Weight (kg)
   - Product Space Area (m^2)
   - Categories of Insulation Material (4 different types: high density EPS, low density EPS, polyurethane, and "custom")
   - Average Thickness (cm)
   - Weight of Phase Change Material (kg)
   - Phase Change Material Start Temperature (°C)

One can use the manipulation of these parameters to match existing ISC models or to produce a hypothetical ISC that matches desired response characteristics based on the Slope Response function.

These tools are described in more detail in sections below, and were referenced in the examples discussed in the main part of this white paper.

I. ISTA Zip Code / Lane Database

ISTA supplies a software tool for input of shipping zip code data. When an "origination point zip code" and a destination zip code are entered, the program function selects the closest corresponding ISTA study lane, by distance, to the inputted zip codes. The equivalent lanes from the ISTA lane study are reported, and the calculated mean temperatures from these lanes are listed.

Origination zip code inputs elicits the closest ISTA study *Inbound* lane and Destination zip code elicits the closest ISTA study *Outbound* lane. A realistic estimate of worst case conditions, in terms of lane average temperature is reflected in the temperatures reported by this software tool, as it relates to the ISTA lane temperature database.

Here are two examples:

Example #1

Input shipping zip codes here					
	↓	ISTA	Mean °C		
	Zip Code	Lane No.	Summer	Winter	
Origination	28210	41	29.4	11.2	
Destination	32506	2	28.1	8.5	
Worst Case			*29.4*	*8.5*	

This case would apply to shipping a ISC from zip code 28210 (Charlotte, North Carolina) to zip code 32506 (Pensacola, Florida). The closest matching *Inbound* lane (from shipping origination point) to a parcel distribution center would be ISTA lane 41. The average temperature for this lane in the summer study was 29.4°C, and from the Winter study was 11.2°C. The closest matching *Outbound* lane from the distribution center to the destination in Pensacola was ISTA lane 2. The average temperature for this lane in the summer study was 28.1°C, and from the winter study was 8.5°C. Making the conservative worst-case assumption, one can conclude that a reasonable data based estimate of transit ambient shipping lane temperature for this shipment would be a maximum of 29.4°C in Summer (at the most extreme part of the year) and a minimum of 8.5°C in Winter (at the most extreme part of the year).

Example #2

Input shipping zip codes here					
	↓	ISTA	Mean °C		
	Zip Code	Lane No.	Summer	Winter	
Origination	75204	70	31.0	7.9	
Destination	99701	1	23.4	3.8	
Worst Case			*31.0*	*3.8*	

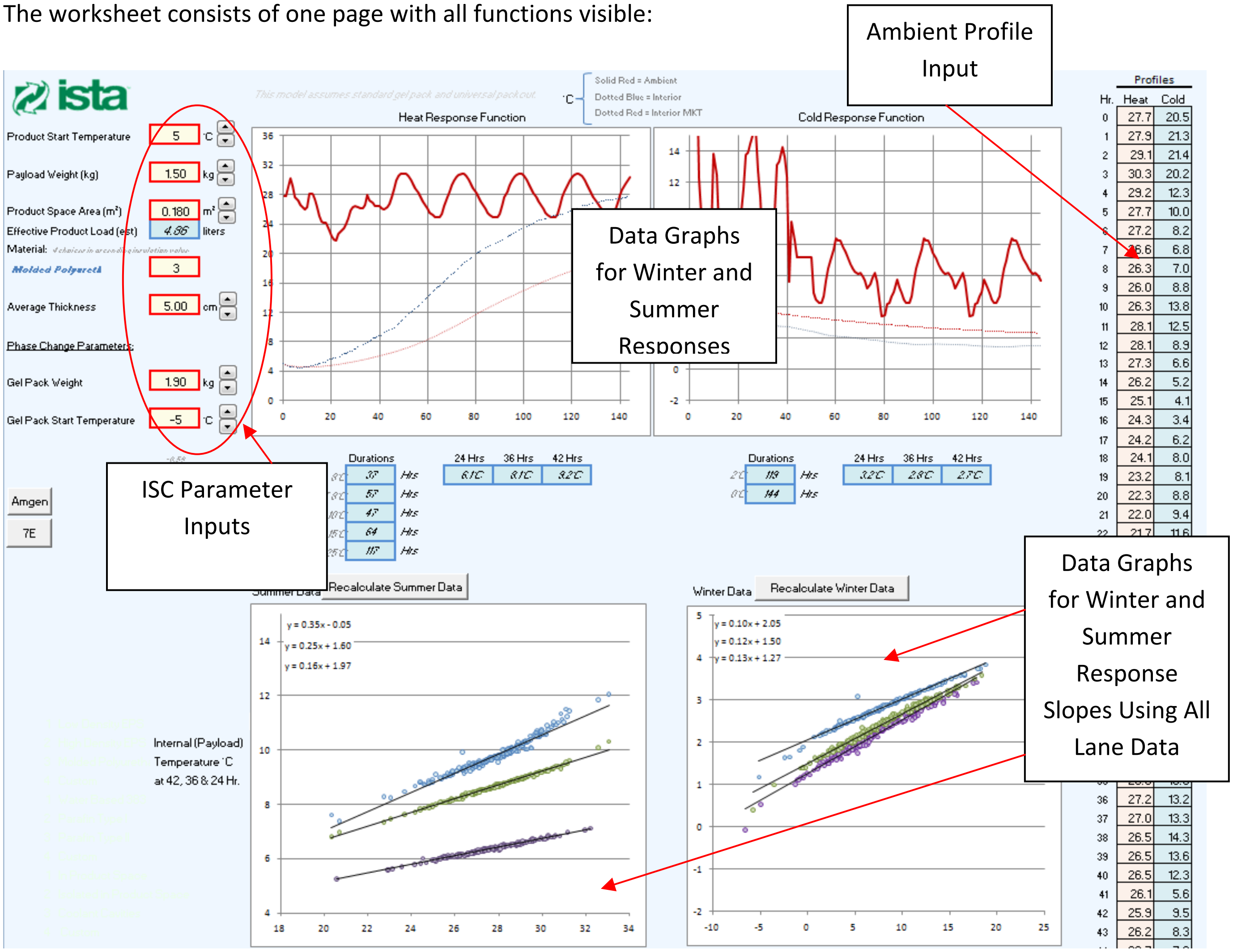
In this case, we are shipping from the Dallas, Texas area (zip code 75204) to Fairbanks, Alaska (zip code 99701). The closest corresponding ISTA study lanes are lane 70 and lane 1. Highest expectation of the summer lane average is 31.0°C and lowest expectation of Winter lane average is 3.8°C.

These values can be used in conjunction with the Slope Response model to determine whether the specific choice of shipper model and shipping thermal criteria will have a high probability of an "in specification" arrival at destination.

II. ISTA ISC Model

ISTA supplies with the package the ISTA ISC Model (designated the Model / Lane Database elsewhere in this append. This software is capable of accepting any ambient profile data in a "cut and paste" data entry method. With profile data in place, one can manipulate various design and packout parameters to ascertain their impact on performance.

The worksheet consists of one page with all functions visible:



ISC Parameter Inputs are performed by "spinners" which gradually increment or decrement values. Ambient profiles can be input by clicking buttons for either the ISTA 7E standard profile or the well-known Amgen profile. Users can also input their own ambient profiles by data entry into the ambient profile columns shown on the right.

At the bottom, there are two graphs that depict the summer and winter Slope responses. These are triggered after the user sets up the desired ISC specification. By clicking on the buttons above each graph, regression lines for 24 hour, 36 hour and 42 hours are generated by the successive entry of all lane data into the profiles column. The plots represent the relationship between the mean temperatures of each lane data set vs. the internal temperature of the designated ISC at each of these time intervals.

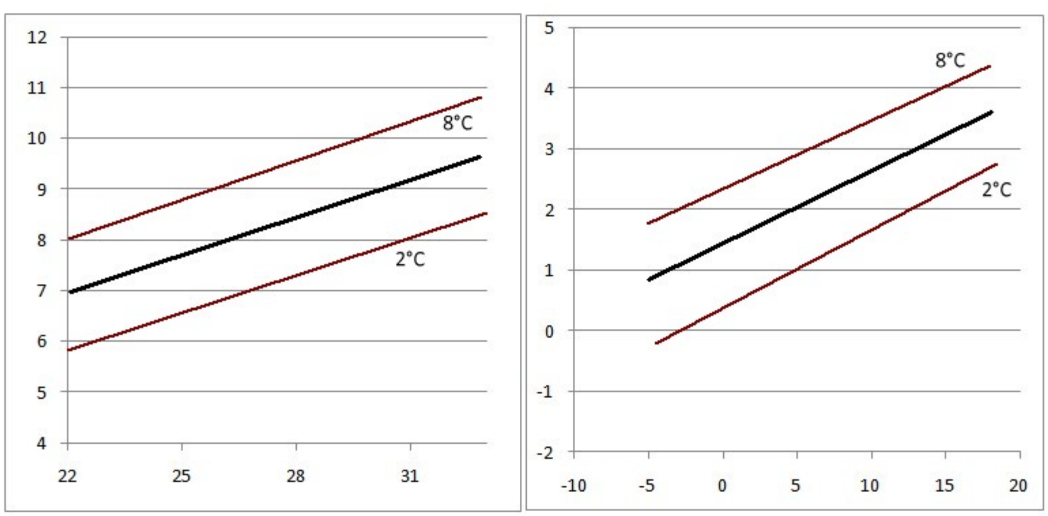
Appendix B - Using the ISTA Slope Response Tools

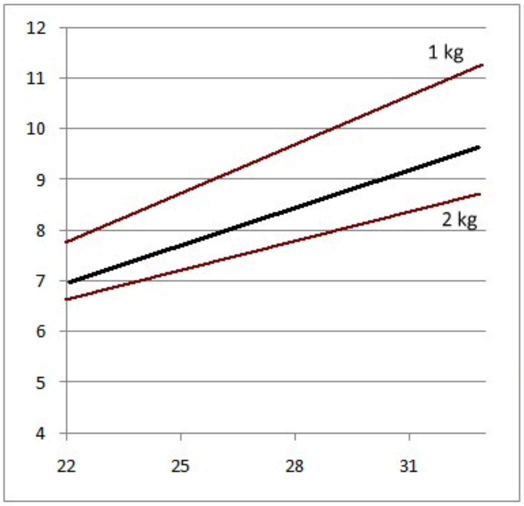
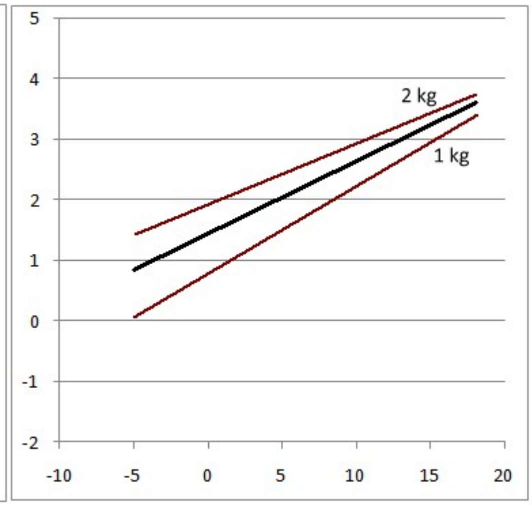
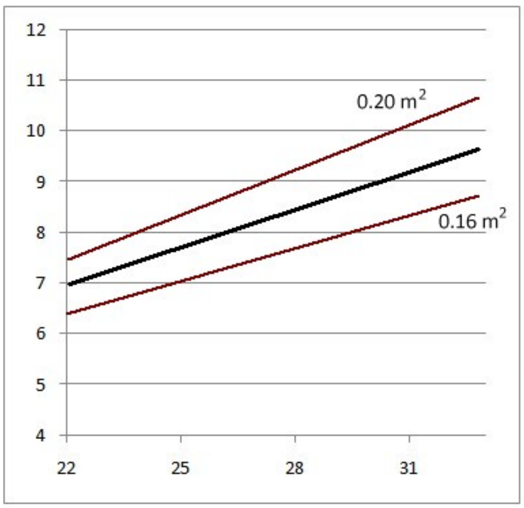
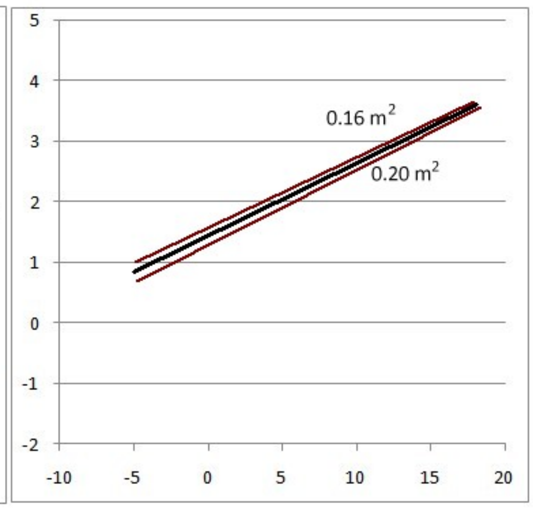
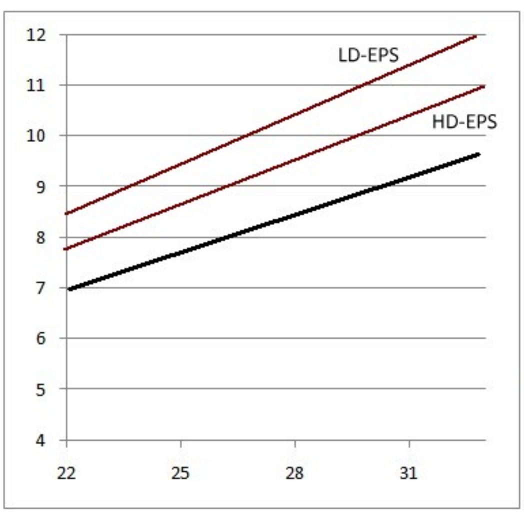
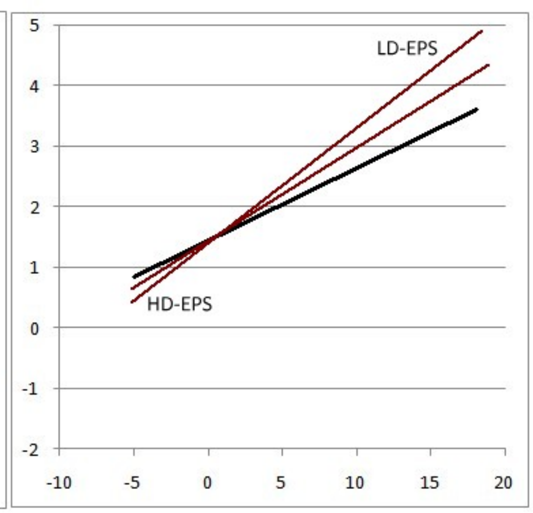
ISTA ISC Model Input Values - Effects on Outcomes

The model used in this ISTA Lane analysis is typical of models that have been used in the industry. The input variables affect the slope function that we have defined in this analysis. For purposes of illustrating how the different input parameters can affect the performance of an ISC, we have started with a defined ISC according to the following parameters:

Parameters	Shipper Base Example
Initial Product Start Temperature (°C)	5°C
Payload Weight (kg)	1.5
Product Space Area (m^2)	0.18
Insulation Material	Polyurethane
Insulation Thickness (cm)	5
Phase Change Material Weight (kg)	2
Initial Phase Change Material Temperature (°C)	-5°C

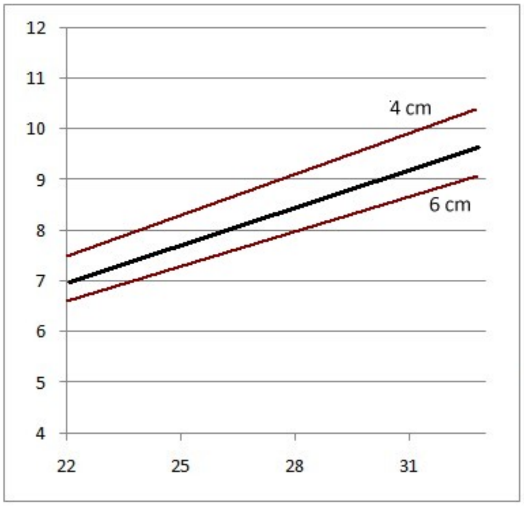
For simplicity, we show comparisons based on the 36 hour response slope function[viii] for the different parameter manipulations. This base example is represented by the black bold line in the following regression plots:

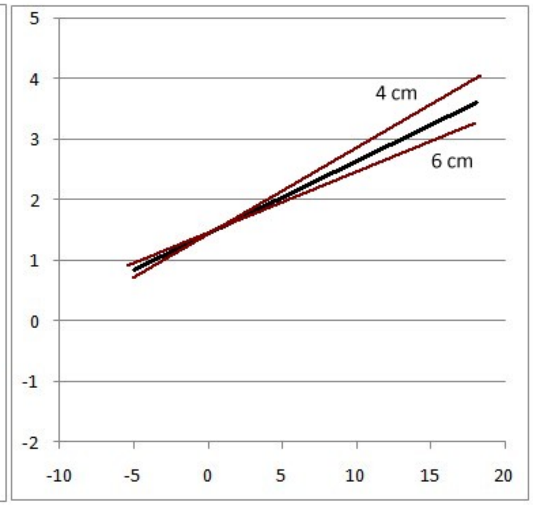
Parameters	Slope Response Function (Summer | Winter)
Initial Product Start Temperature (°C) Base = 5°C	

Payload Weight (kg) Base = 1.5 kg	 
Product Space Area (m^2) Base = 0.18 m^2	 
Insulation Material Base = Polyurethane	 

Insulation Thickness (cm)

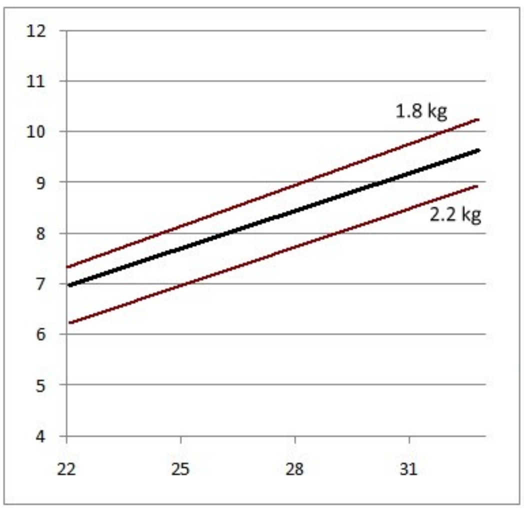
Base = 5 cm

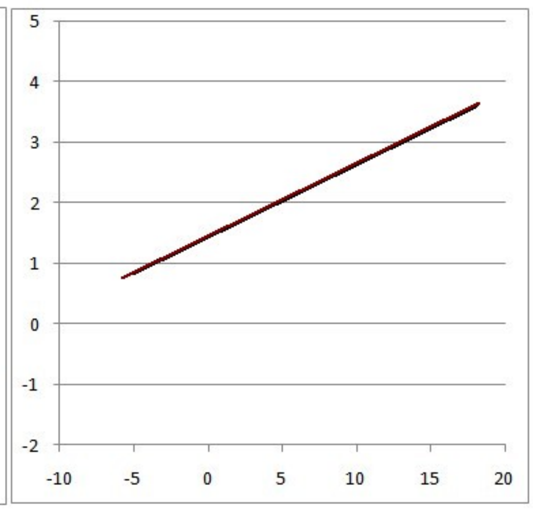




Phase Change Material Weight (kg)

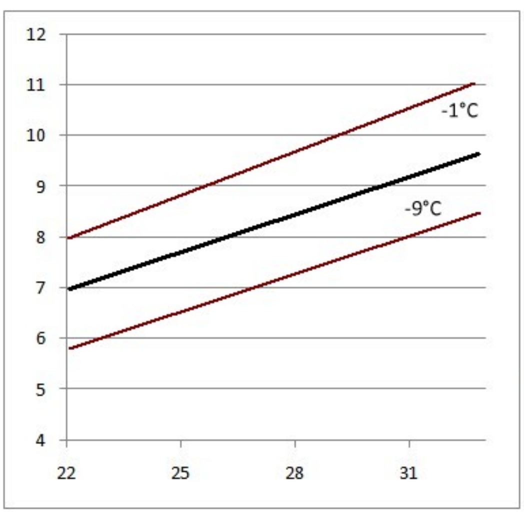
Base = 2 kg

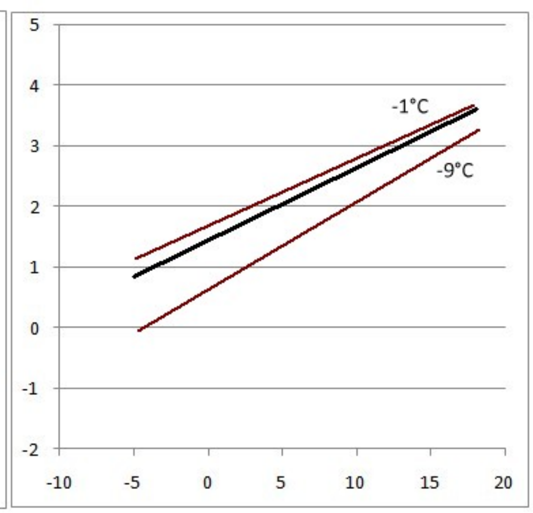




Initial Phase Change Material Temperature (°C)

Base = –5°C





Some of these observations are well known to those who study ISC design and performance. The design parameters (type and thickness of insulation, payload space dimensions) show similar Slope Response patterns with changes in those parameters.

Parameters at least partially under the control of users (payload and phase change weights and starting temperatures) can have a profound impact on performance. Temperature parameters have a direct linear impact on the vertical position of the Slope function, but have no effect on the slope itself.

Weights as "changeable parameters" are different for Payload weight and Phase Change Material weight, Payload (or product) weight affects slope in a very significant way.

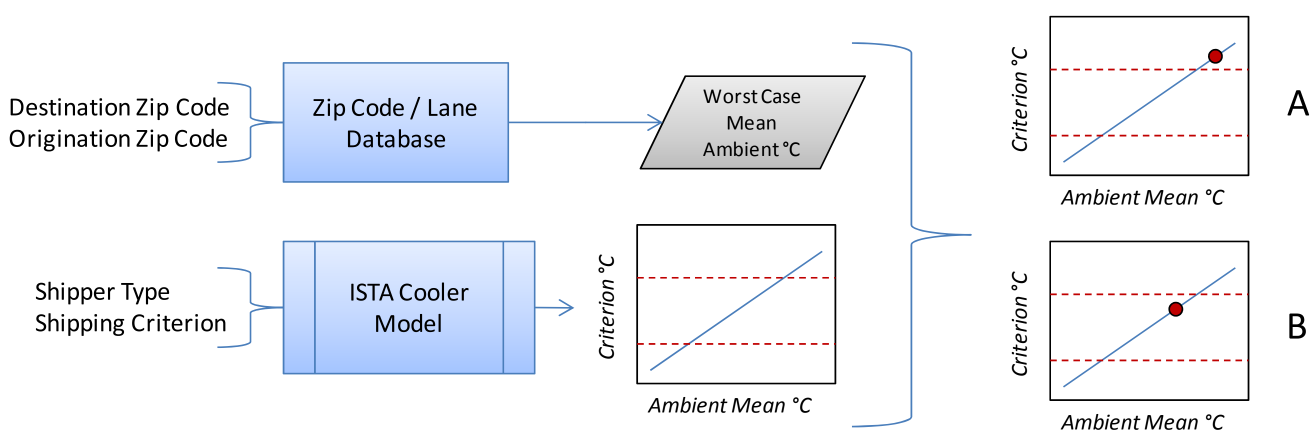
The purpose here is not to explicate these changes as reflected in the ISTA ISC Model program, but simply to demonstrate that ISC parameters can be effectively studied in the context of lane data.

It is important to note that the impact of even small changes in ISC design or packout controlled parameters are greater in scale than the observed "scatter" that we see when actual lane data is used to produce the Slope Response functions. One may reasonably consider that perhaps too much attention is paid to exogenous factors such as profile spikes and oscillations in ambient temperature profiles. Details of ISC packout and ISC parameters are clearly more important.

A Simple Approach to Cold Chain Strategies Using ISTA Slope Response Tools

One straightforward method to use the Slope Model in a cold chain strategy is to filter shipping instances using the zip code information in a way that permits a "yes/no" type of answer to each shipping instance.

When you ship, you know the point of origin and the point of destination. You also know the type of shipper that you most likely will use, and the criterion for maintenance of interior temperature. In simplest form, these variables can be easily processed with the ISTA Lane Data Tools[ix]:



Inputting the geographic data yields an output of the Worst Case data expected for the hottest of summer to the coldest of winter. An internal programmatic process that finds the closest matching lane combination from the ISTA lane database, and returns the mean temperature for that closest match.

A predetermined calculation using the Model program yields a slope plot for the Shipper (ISC) typically used. The mean temperature is then plotted on the Slope function for the Shipper. If the point plots outside the "safe" band determined by the Shipping Criterion, then some action appropriate to that result is indicated ("A" in the above diagram). If the point plots inside the safe zone ("B" in the above diagram), then the shipment is made.

One may employ the logic of this method in a variety of different ways. Here are three examples:

1. Select a shipper type that is sufficiently robust in its performance that worst case shipping mean temperatures always fall within the "safe" band.
2. Create a scenario that an extremely small percentage of typical inputs produce the "A" outcome, as shown above.
3. Run the model in simulations with known geographic inputs until a list of "non-safe" destination zip codes are produced by the designated shipper/shipping criterion combination. Select an "extreme lane" shipper for these specific instances, and have these rare instances flagged for alternate shipper choice at packout.

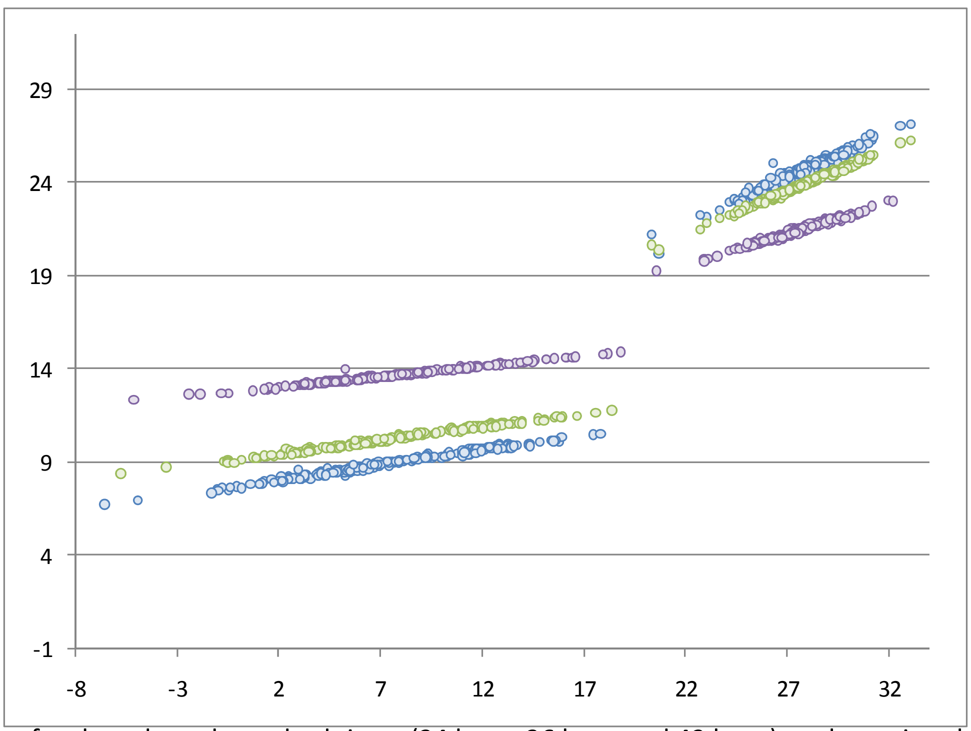
CRT-type Shipments vs. CCT-type Shipments

Most of the discussion and analysis in this appendix have focused on refrigerated shipment. The concepts here can also be used effectively for CRT or "room temperature" shipments. Room temperature ISCs do not need as much thermal protection for CRT shipments when compared to CCT shipments. Here is a typical plot for Winter and Summer Slope response for a CRT shipment:

Using these parameters:

Parameters	Shipper Base Example
Initial Product Start Temperature (°C)	25°C
Payload Weight (kg)	2
Product Space Area (m^2)	0.18
Insulation Material	Polyurethane
Insulation Thickness (cm)	3
Phase Change Material Weight (kg)	1
Initial Phase Change Material Temperature (°C)	-5°C

The following Slope Response was calculated:



The functions are for the selected standard times (24 hour, 36 hour and 42 hour) as shown in other plots. The same conclusions as stated for CCT examples hold for room temperature shipping. If there is a maximum criterion of >30°C and <5°C for the shipment, then we could conclude that 42 hour shipping could use this universal packout for all seasons, for example.

Appendix C - Statement of Proprietary Data Status of ISTA Lane Data

This paper is intended to introduce certain concepts showing the utility of ISTA Lane Data in the formulation of a cold chain strategy for small parcel shipments, and other related types of shipping challenges. ISTA maintains ownership of the data set and associated program material, and licenses these data and the data tools referenced in this paper for a fee to ISTA members. Readers of this document are cautioned that the Lane Data that are the core intelligence of the information presented here is proprietary.

This document is intended as an encouragement to purchase the licensed ISTA lane package. The conclusions, opinions and data analyses presented here may not be used in any other way without written permission from ISTA.

Appendix D - Glossary

TASH - This is an acronym for "Temperature Acquisition Shipper" and refers to a specially engineered corrugated box that was used in the ISTA lane study. Temperature loggers were installed in specially designed slots formed by the combination of two nested corrugated containers with the outer box perforated to accept loggers. Each TASH provided six such slots, one each for the top and bottom, and four sides of the Shipper.

ISC - This is an acronym for "Insulated Shipping Container". This term is used alternatively with the term "ISC" and refers to a box designed for shipping products requiring internal temperature maintenance. An insulation layer that is an integral part of the box maintains temperature. Temperature is maintained by thermal preconditioning of the inserted product and often by means of insertion of a phase change material that is in the solid or liquid form in a bag or container borne internally.

Standard 20 - This refers to a highly structured set of Standard Operating Procedures and Protocols for testing to ascertain ISC performance using the grand average of ISTA lane data as the ambient test profile.

EPS - This is an acronym for "Encapsulated Polystyrene" which is a molded foam material often used in ISCs. EPS is formulated in different densities. The most familiar is the loose structured type of this "Styrofoam" that is the material used for consumer beverage ISCs. This is typically referred to as low density EPS. EPS is formed from styrene beads that are expanded in the manufacturing process. By controlling this process, higher densities can be achieved. Many commercial ISCs use higher density EPS, which has a superior insulation value when compared to lower density EPS.

Polyurethane - This is a reference to the polymeric material that is used in many types of insulation materials. Polyurethane insulation is a rigid or semi-rigid foam material that is either cast in place or used as preformed slabs in the construction of ISCs. It typically has a higher insulation value than EPS.

Phase Change Material - This refers to a mass of material that is installed in an ISC to resist temperature changes. Many materials (water is a common example) have a *high latent heat of fusion*. This means that the materials remain isothermal for a protracted period of time while heat is being exchanged during the melting or freezing of those materials. This isothermal heat transfer aids in temperature stabilization. A typical common term for this type of material is "gel ice" or "blue ice". Many different types are now employed in ISC designs.

ISTA - This refers to the International Safe Transit Association, an industry non-profit organization dedicated to setting standards and testing procedures for transit packaging. See www.ista.org for more details.

Start Temperature - This term refers to the temperature of either the Phase Change Material or the Product at the inception of a shipping event using an ISC. In some refrigerated shipping scenarios, the produce is thermally preconditioned to a pre-defined temperature of 5°C, for example. In the same shipments, one may find a unit or more of Phase Change Material that is preconditioned to a pre-defined temperature of -5°C, for example. Start Temperatures of both types profoundly affect the performance of ISCs during shipping.

Outbound Lane - In the ISTA lane study, TASH units were shipped a central distribution point in Louisville, Kentucky to designated points in North America (see map, page 4). Temperature recording was initiated at the point of pickup in Louisville and terminated at the destination points. The temperature records for these shipments from Louisville are designated Outbound Lane profiles. The word Outbound is italicized in this document to emphasize this specific meaning.

Inbound Lane - In the ISTA Lane study, when TASH units were received at Outbound destinations, with minimal delay, they were reshipped back to Louisville (see definition of Outbound Lane). Temperature recording was initiated at the start of this return shipment and terminated at destination in Louisville.

Zip Code - This is a postal district that is used for USA domestic postal shipping and parcel delivery. Each zip code is a designated geographical zone with known boundaries. Zip codes are 5 digits in length, and constitute rather small districts with metropolitan areas having upwards of 10 zip codes.

Zip Code Centroid - This term refers to the exact geographical point that is at the geometric center of a zip code area.

ISTA Zip Code / Lane Database - This refers to a software function that is performed in an Excel workbook. The software function takes input in the form of shipping origination and destination zip codes. The data returned consists of the mean temperatures of the nearest ISTA Lane profile, Winter and Summer season that correspond to the inputted zip codes. The function consists of two parts: (1) finding the equivalent zip code of a standard ISTA Lane Study lane, and (2) retrieving the mean temperature from that lane. The workbook incorporates distance information between zip codes based on know Zip Code Centroids. Mean temperatures are based on 50 hour averages for the lanes that the program selects as the nearest lane equivalent.

ISTA ISC Model - This refers to a software function that is performed in an Excel workbook. The software function consists of a generalized model of ISC performance. Design and operational parameters and a designated ambient profile are inputs (see full description in Appendix A, section entitled “II. ISTA ISC Model"). The output is a time based function that tracks changes of temperature in the product space of the ISC. The software function also permits the calculation of Response Slope functions by successive runs of the model with individual lane profiles from the ISTA Lane Study.

CRT - This refers to Controlled Room Temperature, which is a defined set of conditions intended to put quantitative limits to" room temperature" as it applies to the shipping and storage of pharmaceutical products. It was originated by the U.S. Pharmacopeia. The standard definition is " A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° C to 25° C (68°-77° F) that allows for brief deviations between 15° C and 30° C (59°-86° F) that are experienced in pharmacies, hospitals, and warehouses. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording. An article for which storage at Controlled room temperature is directed may, alternatively, be stored in a cool place, unless otherwise specified in the individual monograph or on the label."

CCT - This refers to Controlled Cold Temperature, or more recently "Cold". The working definition is "Any temperature not exceeding 8°C (46°F). A refrigerator is a cold place in which the temperature is maintained thermostatically between 2°C and 8°C (36°C to 46°C)." Generally this 2°C to 8°C range is a commonly accepted definition because many of the products in storage and shipment must be protected from freezing, as well.

Average Thickness - This is a term used in the ISTA ISC Model that refers to "effective thickness" of the insulation of an ISC. Actual ISC designs often show areas with thicker insulation in some parts and thinner in other parts. Shapes may be complex, so determination of "Average Thickness" may be an estimate of the equivalent thermal protection if the shape of the ISC was a simple box with a uniform layer of insulation all around.

Appendix D - References and Endnotes

References

This section lists only those references that are relevant to the discussion and citations for attribution of quotes. It is not intended to be a comprehensive list of references in the technical fields touched upon in this paper.

Sandy Cook, President Thermal Packaging Solutions, "*Gap Analysis, operational procedures for the storage, handling, and distribution of temperature sensitive medical products*"

Larry Gordon, President, Cold Chain Technologies, "*Minimizing loose ends,- supporting distributors in the cold chain*" both Presentations at the Advanced Cold Chain Management and Distribution for the Regulated Industry Workshop, La Jolla, California 1/30/2007

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Claudia Okeke, "*Current USP activities on packaging, distribution and storage relating to cold chain issues*" Presentation at the Advanced Cold Chain Management and Distribution for the Regulated Industry Workshop, La Jolla, California 1/30/2007

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Rick Garafolo, Process Improvement Manager, Wyeth Pharmaceuticals, "*Understanding the how's and why's of developing time and temperature cycles for qualification studies of cold chain shipments*" Presentation at the Advanced Cold Chain Management and Distribution for the Regulated Industry Workshop, La Jolla, California 1/30/2007

Ümit Kartoğlu, *"Model requirements for the storage and transport of time and temperature sensitive pharmaceutical products"* WHO Working Draft, November 2010

Endnotes

[i] ISTA 7E profiles and an overview of the Lane Data have been presented in several symposia and meetings: BioTech Supply Chain Academy, San Francisco, California 2009; ISTA China Symposium, Shenzhen, China, September 2009; PCCIG-PDA Pharmaceutical Cold Chain Management Conference, Bethesda, Maryland, March 2009; ISTA International Transport Packaging Forum, Orlando, Florida, March 2010; The Pharmaceutical Supply Chain Summit, Baltimore, Maryland, June 2010; International Association of Packaging Research Institutes World Conference, Tianjin, China, October 2010; IQPC-Philadelphia, Pennsylvania, September 2010; IQPC-Toronto, Canada, February 2011; ISTA International Transport Packaging Forum, Orlando, Florida, April 2011 (Don Wilson, Amgen). ISTA Report 0043 by William Pelletier of University of Florida is the original data presentation of the averaged profiles.

[ii] Derived from National Weather Service website data. See http://www.weather.gov.

[iii] These are averages that are either 72 hours or less, depending upon the length of the recording episode. Most temperature profile data sets terminate at delivery from 30 to 55 hours of duration. Both *Inbound* and *Outbound* data are used with a single numeric lane reference number. Elsewhere in this analysis, averages are computed to 24, 36 or 42 hours for purposes of demonstration of the Slope Response function, and *Inbound* and *Outbound* lanes are treated as separate cases for the Slope Response function computation.

[iv] See Appendix C for a complete explanation of data tools related to zip code cross-referencing that are supplied with the ISTA lane data package.

[v] Presented by Paul Harber at 2011 IQPC 9th Annual Cold Chain & Temperature Management Summit, Toronto, Canada, on February 22-24, 2011. The author acknowledges invaluable contributions from Paul Harber in the formulation of many of the concepts used in this presentation. Paul's comprehensive knowledge of Pharma Cold Chain issues cannot be overemphasized.

[vi] Note that the full duration averages are slightly different from the 50 hour averages used in this analysis.

[vii] ISTA supplies the software tools described in this paper, but does not release program code or access to certain functional parts of the workbook that perform the calculations. These are proprietary. Users requiring modifications may apply to ISTA to obtain consulting assistance to modify or integrate the functions of the program tools.

[viii] The vertical axis represents internal ISC product temperature at 36 hours. This is plotted as a function of average lane temperature for 36 hours (X-axis). All lane points are used (Inbound and Outbound) and the line that appears is a regression line fitted to the data.

[ix] The "Outcome °C" on the Y-axis represents the internal temperature for designated durations. The model uses 24 hours, 36 hours or 42 hours as standard durations. The "Ambient Mean °C" axis represents the mean temperature for those durations for specific lanes in the ISTA lane database.