

This article discusses the need for special procedures starting at receipt of sensitive components/ ingredients, through operations and distribution, including requirements and new packaging supplies for temperature sensitive medical products.

# Operational Considerations of Thermally Sensitive Healthcare Products

by Sanford L. Cook

## Introduction

The rapid pace at which new medical products are being tested and coming to market has become a challenge that product managers, logistics and engineering professionals are confronted with at an accelerated rate. Technologies that protect these precious materials from potential environmental assault should be understood in their respective portfolios. A growing awareness of the degrading effects to products resulting from exposure to temperature and humidity has caused special considerations throughout all phases of operations. There are some basic and salient points that the plan leader should bear in mind - *Figure 1*.

This article describes the special considerations operations personnel and clinical project managers are tasked with when designing a cost efficient strategy to facilitate the safe acquisition of raw materials, formulation pro-

cesses, manufacture, packaging, storage, and distribution of temperature/humidity sensitive materials. Discussions will include understanding the physical forces products are exposed to, transportation, manufacturing equipment qualifications, and monitoring, as well as strategic planning from the receiving dock to the shipping dock.

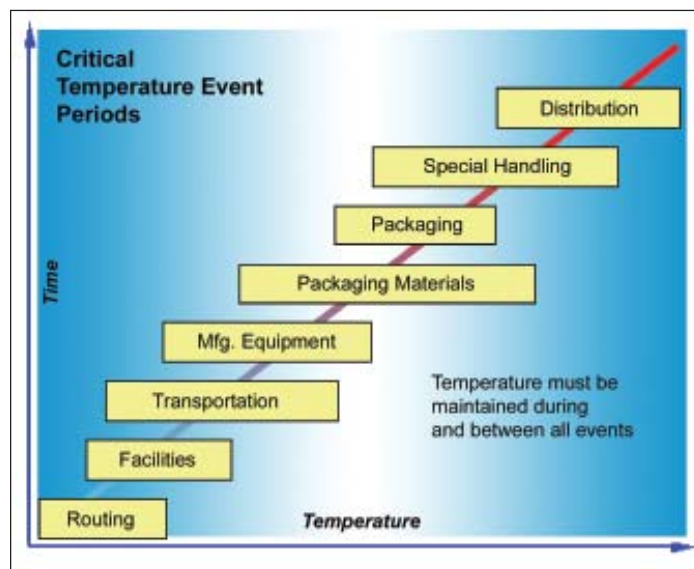
## The Influence of Weather

Weather reports predict the results of physical forces in the atmosphere. The dynamics created as a result of rapid temperature differences may produce ancillary products such as moisture (rain) and negative or positive pressures (winds). Through technical means (discussed later in this article), a potential for stormy weather is produced inside an insulated container.

This example of weather may be illustrated in packaging as follows: temperature sensitive

products are placed into insulated containers to protect them from ambient conditions. If the products must be kept at refrigerated or freezing temperatures, refrigerants, such as dry ice (CO<sub>2</sub>) or Phase Change Materials (PCM), are used to drop the temperatures inside the protective box. The package is sealed. As the cold dry air is expunged from the refrigerant, it will collide with the warmer air trapped when the box was closed. As the temperature drops around the product, the moist air surrounding the product releases any moisture that it can't hold. The

Figure 1. Critical temperature event periods.



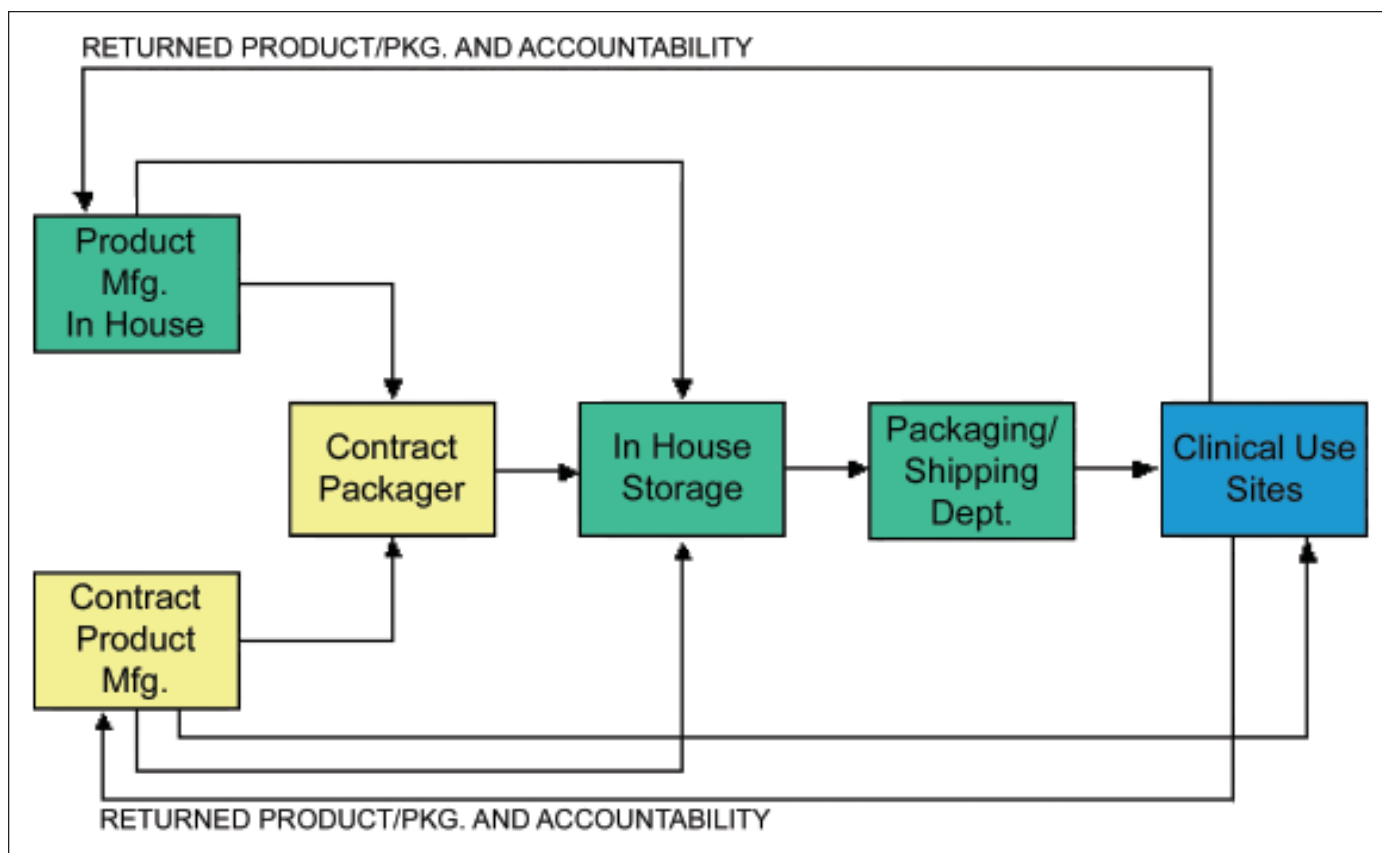


Figure 2. Clinical product distribution chain.

condensation may be controlled by proper design. All factors must be considered when designing a complete system to protect sensitive products. However, a system or “protective tunnel” should start long before the finished product is packed into insulated shipping containers and all aspects of the product’s processes and journey should be considered.

## Incoming Components

Each step should be analyzed as a detail to a complete system. The system must be continuous and not allow any part to fall between the cracks. For example, how do the basic ingredients arrive at the processing facility? If at least one component is temperature sensitive, there should be a process to check to see if that component has been exposed to dangerous temperatures or over excursion time durations during the shipping event. Single exposures may not be as important as the cumulative time the product has been exposed. Normally, there will be labeling depicting the temperature tolerances; however, a device should be included that will indicate any time/temperature variances. *Responsibility should be assigned to specific personnel to ensure the materials arrive as specified on the label or accompanying documents.*

Of course these steps should be detailed in Standard Operating Procedures (SOPs) as part of an overall protocol. The next step is not always accounted for when the material arrives. Specific procedures and responsibilities should be assigned to material handling in terms of exposure time documentation from the dock to the temperature-controlled environment.

## Facilities

Most storage facilities today are adequately temperature controlled and monitored. However, when the products are taken from these areas on their way to an operation process, the exposure time from storage facility to the operations room is not always accounted for. Environmental *gaps* may exist that start the cumulative exposure time to degrading temperatures. Of course, the exceptions are when the entire operations facility is environmentally controlled to label temperatures, but that is pretty rare.

There should be a document and responsibility record that tracks the time/temperature during these material handling events added to the overall SOP.

Assuming that the operations room where the actual formulating or manufacturing process is being done is being done is temperature controlled, the equipment that is used in the process should be validated to operate at the specific operational temperatures. Equipment that generates heat is often overlooked. Therefore, products may be exposed to machine generated temperatures during the process, even though the machines may be validated to be operational at given temperatures. The Installation, Operation, and Qualification (IOQ) of equipment should have provided certification of the validation. Included in the documentation should be data that depicts the time and the rise in temperature of the product during equipment normal running time as well as stoppages. Often, the characteristics may change and cumulatively affect the product.

In many cases, *primary* containers or the containers that

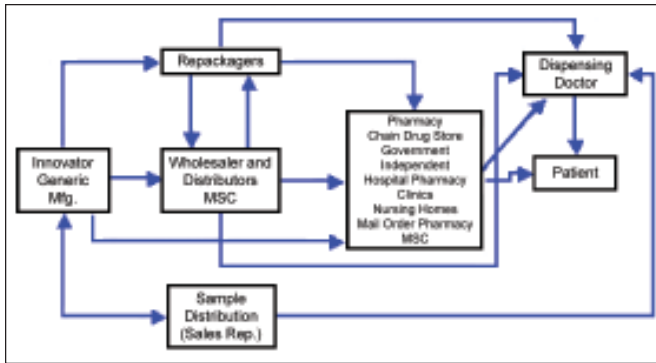


Figure 3. Pharmaceutical distribution chain.

the pharmaceutical product is actually touching such as a vial, blister pack, card packet, etc. and the *secondary containers* used to group and hold the primary containers in a “package” have been filled as part of the manufacturing process. After they are filled, these containers must now be transported to holding/storage facilities. Again, the transporting operation must be accounted for in terms of time/temperature as well as the validation certifications for the actual operations (manufacturing and filling), holding/storage facility, and the associated equipment as described above.

In the case of clinical supply groups, although the manufacturing process may not be relevant, the material handling procedures are very highly significant as to the products final efficacy - *Figure 2*.

## Packaging and Packaging Material Considerations

Secondary containers (as described above) that are normally chipboard (cardboard) or thin corrugated boxes are then taken out of the storage facility and readied for tertiary, insulated, and protective packaging for shipping. There are many types of protective shipping systems that are available from specialty suppliers. However, any system used must be validated to ensure the protection of the product from environmental damage. Depicted in *Figure 4* is a shipping system



Figure 4. Shipping system.

that contains insulated boxes, Phase Change Materials (PCMs) sometimes referred to as “gel packs and described below”), data loggers, heat sink materials, and in some cases, shock absorbing components. The configuration of the packaging components and total system is crucial to keep the products safe during shipping - *Figure 5*. If you do not have a qualified thermal packaging specialist in house, there are highly experienced independent consultants available that are not obligated to specific suppliers products and offer objective advice since they are actually working for you. (A source for independent consultants may be found at the Consultant’s Council listed on the Institute of Packaging Professionals (IOPP) Web site. [www.packagingconsultants.org](http://www.packagingconsultants.org).)

An empirical validation test by an approved, independent laboratory, experienced in temperature controlled packaging and regulatory requirements, should be conducted - *Figure 6*. (Some suppliers provide these services. However, validation tests should be conducted at arms length by independent laboratories. The use of “pre-validated containers” is not recommended, but if used, be sure the supplier will certify that your specific shipping depiction for each packout meets their certification in a written and signed statement.

Insulation materials are a function of shipping duration

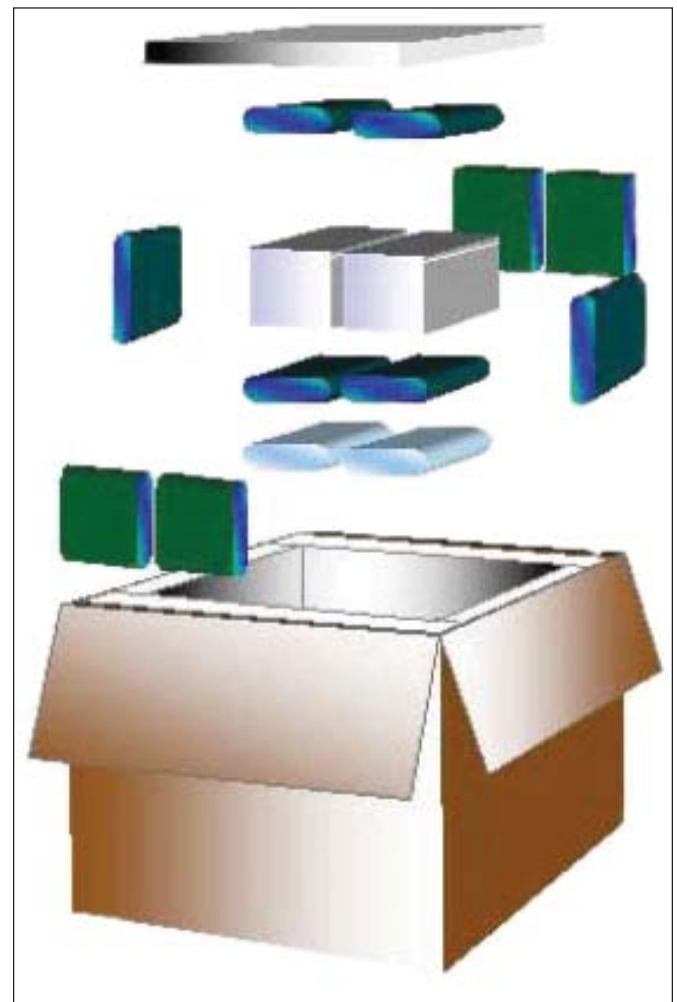


Figure 5. Configuration of packaging components.

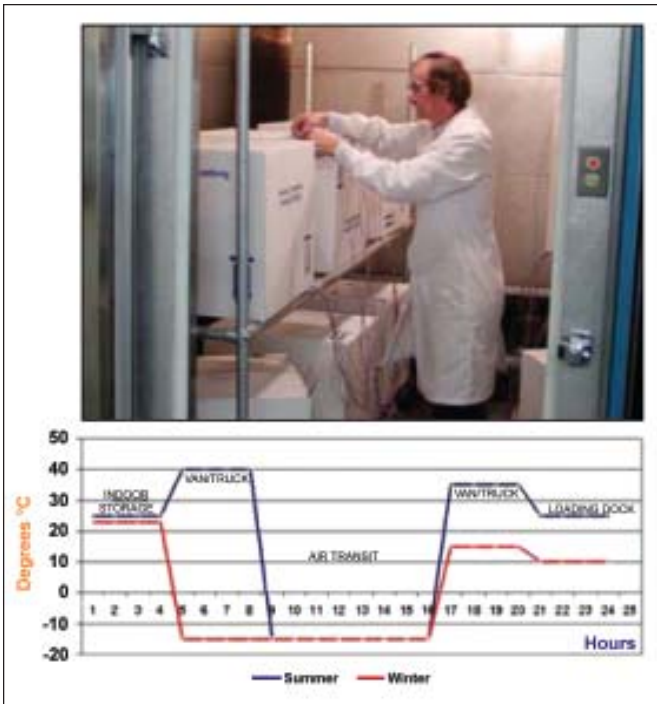


Figure 6. 24-Hour shipping profile.

time, anticipated ambient temperatures, label temperatures of the medical product, and PCM components used internal to the packaging system. The thickness of the insulation may vary depending on the volume of the stabilizing materials. (There are simple mathematical models available to determine the best materials to use.) - *Figures 11 and 12*. Until recently, most insulation materials used were foamed plastics, Expanded Polystyrene (EPS), or urethanes. We have actually tested and specified materials that have the same or better conductivity strength, are lighter (hence less expensive to ship), take up less space, have more puncture resis-

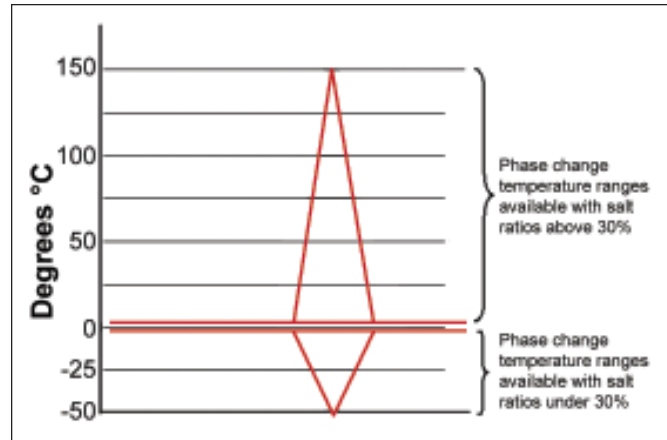


Figure 7. Phase chart - salts added.

tance, and are acceptable in all countries without financial penalties due to environmental concerns. The materials work out to be far less costly than traditional foamed plastics and in at least one case, the manufacturer is currently supplying several healthcare companies in the US and Europe.

PCMs are materials that change their physical state due to temperature. The type used in this discussion are basically water, therefore will turn to a liquid or “phase-change” when exposed to temperatures above 0°C. They solidify to ice at temperatures at or below 0°C. During the time the ice is still solid, the temperature will remain at a constant 0°C. The time the solidified, frozen water, ice type PCM is taken from below 0°C temperatures storage areas to above those temperatures is the “Heat of Fusion.” (See definition and discussion at the end of this article.) Depending on the mass of the PCMs in relation to time, product, insulation and ambient temperatures, the internal temperatures will remain constant. The reverse is also true; these types of PCMs, like water, will solidify or “phase” to a solid state below 0°C - *Figure 7*.

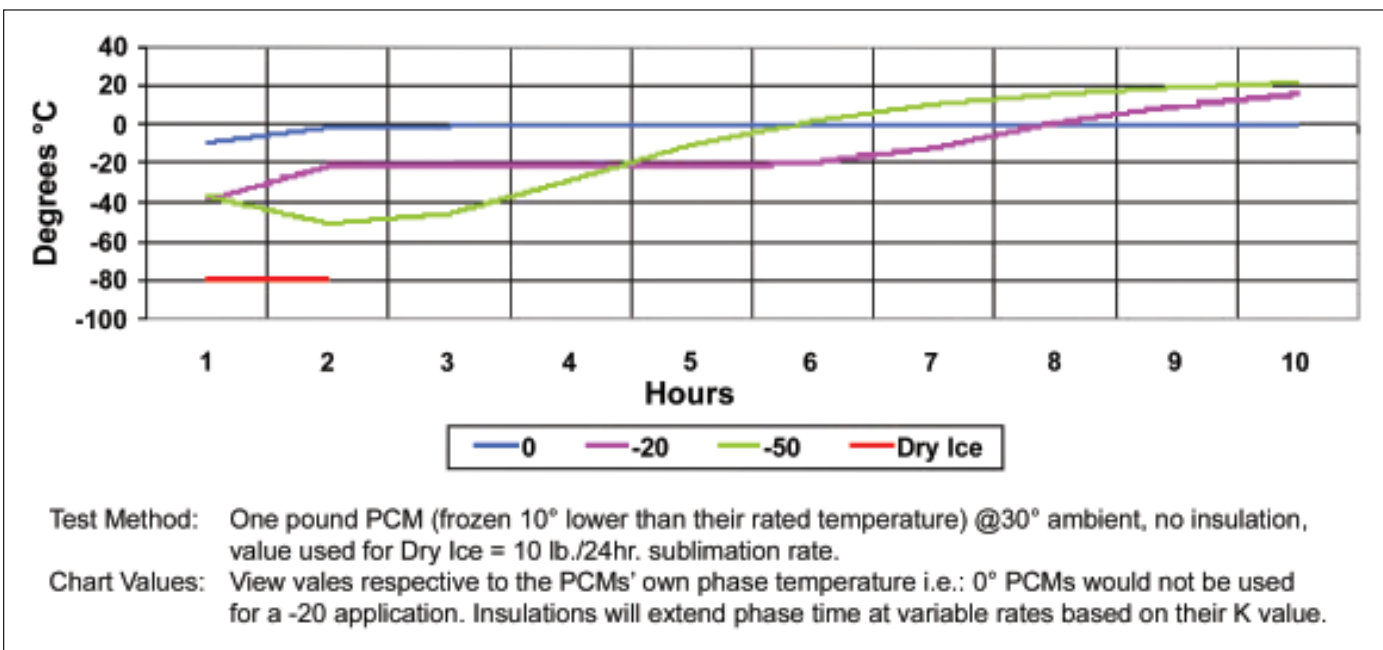


Figure 8. Phase change material comparison.

Type	Temperature Range	Note	Usage
Sponge/Water	0°C	Retains its shape when frozen, leaks easily	Used for <0°C, 2°C to 8°C, and above 8°C temperature ranged products
Phenol Foam/Water	0°C	Retains its shape when frozen	
Hydroscopic Polymers (Gel)	-10°C to 0°C	Widely used industry standard available in various outer wrap configurations	
Hydroscopic Polymers/added salts	-45°C to +26°C	COLD - Could replace some dry ice applications WARM - Help maintain room temperatures	
Paraffin	26°C to 60°C	Maintain room temperatures	

Table A. Phase change materials.

There are specialty PCM products available that will actually stay solid at various specifically controlled temperatures - *Table A*. For example: PCM formulae may remain at +4, +30°C or even above. Others remain constant at -10, -20, or lower. Products labeled temperatures from 2-8°C may utilize these PCMs. Products that are to be kept below -10 or -20°C can use the low temperature versions. (Dry ice is still required below -30°C.) There are pluses and minuses associated with using common type or specialty PCMs. In Figure 8, there is a comparison in the time it takes one pound (.45 kilograms) of various temperature PCMs and dry ice to phase from a solid to a liquid. Using mass multiplied by time, the chart should give a good indication of the expiration rate for each type. The phase time in this example assumes room temperatures approximately 65°F (18°C.) and does not take insulation values when placed in a closed container into consideration. A thermal packaging expert should be consulted for the most efficient solution as to which type to use.

Whether or not a validation test is performed, a temperature monitor/data logger should be used as a safety factor. There are various types of indicators and monitors. Chemical indicators are one time, line of sight devices with no memory. *What you see is what you get*. The upside is that they are inexpensive. The downside is that they trip at a fairly wide tolerance of temperatures and may not be depended upon to indicate when the critical failure temperature was reached. These indicators should not be used for archival purposes, particularly for tight temperature tolerance, sensitive, and valuable medical products. Electronic devices vary as to cost quite broadly. The benefits are that they are very accurate, normally within +/- .5° C; provide a precise record of temperatures, humidity when required; may be archived and encrypted in accordance with 21 CFR Part11; and make available many types of alert signals-digitally and line of sight - *Figure 9*. Technology is changing rapidly in the electronic devices. There are products available that provide all of the information listed above in addition to a reduced size (approximately the size of half dollar coin), may be downloaded into a computer individually or added to other UPC logistic and anti-diversionary information, and monitored from a wireless remote location at any time during shipping or storage. In addition, the device has ranges down to and including -80°C and is less costly than most temperature data loggers presently offered. It is recommended that electronic data loggers be used even when the packaging has been validated for the assumed ambient weather exposures. Sim-

ply said, we believe all protective packaging should be empirically endurance tested for actual anticipated applications; however, on the rare occasion that the package is exposed to extraordinary conditions, the product may still be acceptable. The monitor will be the only evidence to save the shipment or have to reject it decisively at these latter unexpected events. Electronic devices may now monitor temperatures and locations even when diverted. Other inexpensive devices are available that provide end user verification.

Risk management should be employed when considering to either validate by laboratory testing a protective packaging system or to merely monitor each shipment. We believe that a properly tested system will give reasonable assurances that the product will remain within label temperatures throughout the shipping event and all subsequent shipments of similar materials and products. The endurance test is



Figure 9. 21 CFR Part 11 compliant.



Figure 10. Certified test report.

performed with the proposed packaging design in a temperature controlled test chamber at programmed predetermined temperatures to which the package will likely be exposed. Smaller or medium size packages are also tested in various physical attitudes, such as on their side and upside down, if appropriate, during the test to simulate material handling on trucks or aircraft. The certified test report that is published is an archived document that will serve as evidence that the protective packaging is appropriate for the applications investigated. The report should include a detailed description of the validated test equipment, packout depiction, and test results - *Figure 10*. Monitors by themselves, provide a “snapshot” of that particular shipment and do not provide assurances until after the event that the products will arrive safely at their destination. (Too late if out of tolerance.) Therefore, the laboratory validation test to predict a successful shipping event for valuable and high occurrence shipments in terms of weather environments and handling in addition to repeatability of such success is recommended. Shipments that are of low occurrence and low value may be considered for monitors exclusively.

## Packaging Test Protocol and SOP

Documents must be generated to precisely depict the purpose and scope in addition to all of the shipping, handling, and ambient environment events that are expected to occur to measure the endurance to protect products during shipping and storage. Precise identification and traceability of packaging materials and medical products must be included. *The text should include all supporting documents that are needed such as temperature profiles, packaging configurations, quality standards (company and appropriate regulatory), relevant policies, and specific assignment of responsibilities by step, segment, and in total.*

## Distribution

Commercial products and clinical studies vary in actual operations and distribution - *Figures 2 and 3*. However, in terms of temperature control, the two delivery systems have identical requirements. The protective packaging design will be the same. Whether packaged internally or at a contract packager, the responsibility and protocol/SOP documentation must be controlled by the owner of the project. For example, even if the packaging and distribution is actually done at a contract packaging company, the responsibility for clear and precise protocols, SOPs, material lists, and any other required documents is still the project manager's. The Project Manager may designate others such as the logistics manager to generate protocol/SOPs and manage their segments.

## Quality and Regulatory Guidance

Whether products are manufactured in the US or the European Union (EU), all processes, personnel training, and equipment qualification must be followed in accordance with current Good Manufacturing Practice (cGMP). The guide for US regulations is found in the Code for Federal Regulations (CFR). Chapters 21 CFR Parts 210 and 211 include regulations for processing, packing, or holding of drugs and finished pharmaceuticals. Medical devices are covered in 21 CFR Part 820. Qualify testing methodology is covered in 21 CFR 211.60. The US Food and Drug Administration (FDA) is responsible for ensuring that products consumed in the US are produced and marketed to approved standards, regardless of the origin of manufacture. The federal government Agency audits the phases of biopharmaceutical development through all stages of manufacturing, testing, and initial distribution. There must be sufficient evidence that drugs and other related pharmaceutical products have been adequately tested to perform as purported and have a relative degree of safety during human usage. [www.fda.gov](http://www.fda.gov).

The United States Pharmacopoeia (USP) is a quasi-government organization that is composed of regulatory agency personnel, academia, and industry groups interested in pharmaceutical standards. USP journals and periodic discussion groups generate proposals and guidelines. USP Resolution 10 is a guide for storage and shipment. When marketing in Europe, standards are produced by EU, European Economic Commission (EEC) Council Directives for products consumed within the European Community. As an example, 75/319/EEC is a standard that relates to analytical, pharmacological/clinical standards, personnel, premises, equipment, documentation, production, quality control, complaints, product recall, self-inspection, and testing. There are several amendments to the basic document and all are listed on the EC Web site. An interesting Web site to visit is at: <http://ts.nist.gov/ts/htdocs/210/gsig/eu-guides/sp951/sp951.htm>, “NIST Special Publication 951 - A Guide to EU Standards and Conformity Assessment.” In the table of contents, there is a link to “Standardization in the EU and the United States: A Comparison.” Most notably is a general statement that in Europe standards are developed centrally and in the US by sector.

## The Plan

1. Gather product stability data
  - 1.1 Ensure documentation exists
  - 1.2 Ensure documentation is defensible
2. Define manufacturing, storage, and distribution environment
3. Map current or proposed product stream
  - 3.1 Collect all relevant protocols and SOPs applicable to processes, personnel, facilities, and equipment.
  - 3.2 Ensure there are complete SOPs for each step in the product stream
4. Define vulnerabilities of current documentation and systems, including gaps in material handling, movement, and processes.
  - 4.1 Evaluate effectiveness of current procedures SOPs.
  - 4.2 Develop new and/revise appropriate SOPs to adequately describe all procedures and methods required to achieve successful cGMPs.
5. Collect/develop all validation reports and documentation required for materials and equipment.







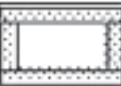

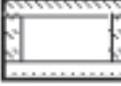
Heat Test (30°C) with 500 ml water (5°C) and 1 x 32 oz. Frozen Gel Bottle (-18°C)										
Container	Insulation	k	wall thickness	R Value	Hours <10°C	Hours <20°C	Weight ACT/Dm	Est. Mat. Costs (500 qty) \$		
								Cost	Gel	Total
Corrugated Only 	none	---	C Flute	---	2.5	17	4/4 lbs.	\$0.75	\$1.00	\$1.75
Fabric Tote 	Thinsulate Style	0.25	3/4"	3	8	23	4/4 lbs.	\$9.40	\$1.00	\$10.40
Molded Cooler 	Rigid Polyurethane	0.14	1/2"	3.5	3	24	6/6 lbs.	\$15.40	\$1.00	\$16.40
Corrugated w/Bubble 	Astrofoil double bubble foil	0.19	5/6"	3.3	6	27	4/4 lbs.	\$6.00	\$1.00	\$7.00
EPS KD 	EPS 1.5 lb. Cu. ft.	0.25	2"	8	13	32	5/11 lbs.	\$5.00	\$1.00	\$6.00
EPS Molded 	EPS 1.5 lb. Cu. ft.	0.25	2"	8	12	30	5/11 lbs.	\$5.50	\$1.00	\$6.50
Polyurethane KD 	Rigid Polyurethane	0.14	2"	14.3	26	48	7/11 lbs.	\$12.00	\$1.00	\$13.00
Polyurethane Mid. 	Rigid Polyurethane	0.14	2"	14.3	26	48	7/11 lbs.	\$16.00	\$1.00	\$17.00
Vacuum KD 	Vacuum Panels	0.04	2"	50	54	80	10/11 lbs.	\$44.00	\$1.00	\$45.00

Figure 11. Thermal comparison profile-insulation materials.

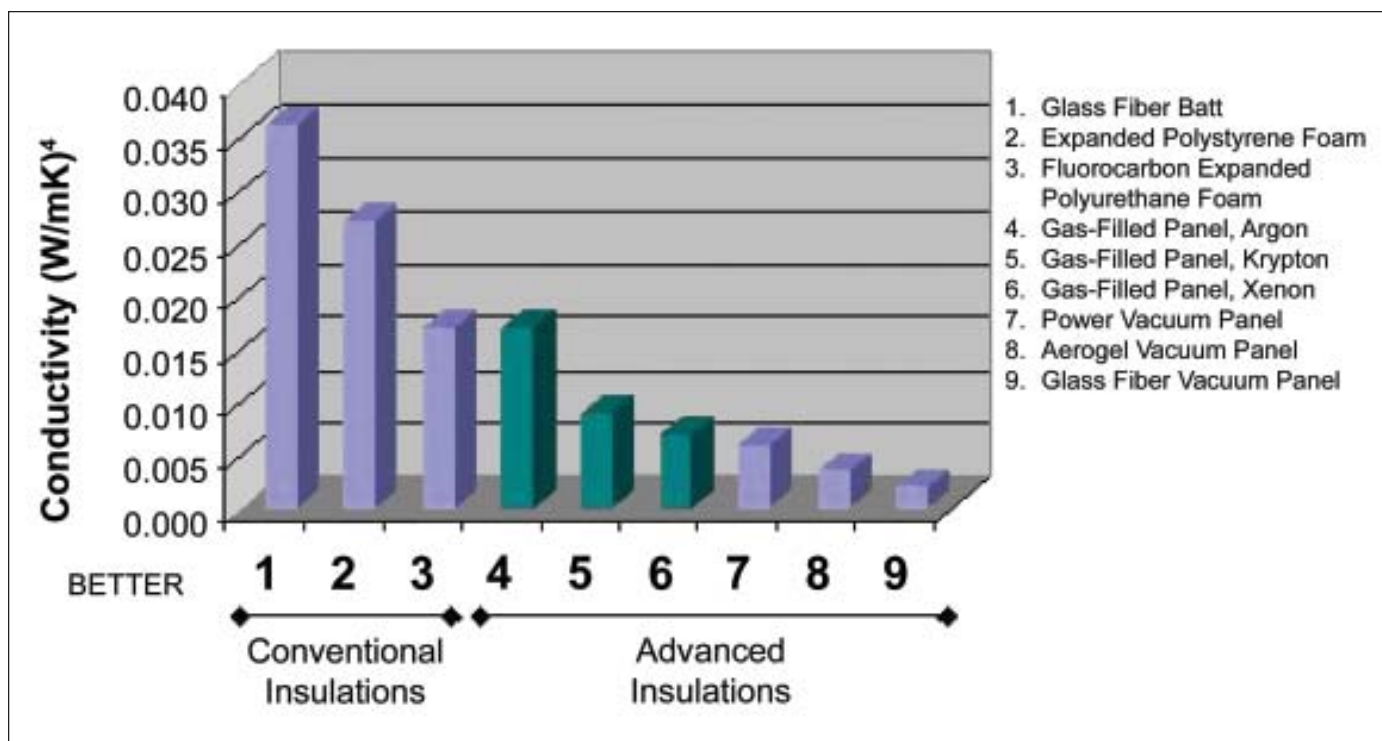


Figure 12. Performance data for conventional and advanced insulations.

## Conclusion

Relevant to the history of the biopharmaceutical industry in the US and Europe in terms of time, the recognition that medical products may change their efficacy of their products for the worse due to temperature has been very short. Storage and packaging studies have evolved recently to generate highly effective procedures and materials. Each segment of the manufacturing and clinical test distribution process has recently been highly visible. Appropriate training, material familiarization, and validation studies have moved higher in priority by industry and regulatory agencies. However, there may be unprotected gaps in the procedures that commence at the actual receipt of ingredients and between each phase of the product cycle.

Material handling and movement between processes should be accounted for to guarantee that temperature excursions do not exceed acceptable accumulated exposure levels before and in addition to storage and packaging.

We need to ensure that product evaluations and effectiveness are not compromised at any point from receipt of components, manufacturing operations, clinical studies, and through all segments of distribution.

## Heat of Fusion: Definition and Discussion

The **standard enthalpy change of fusion**, also known as the **heat of fusion**, is the amount of heat energy which must be absorbed or lost for 1 gram of a substance to change states from a solid to a liquid or vice versa. It is also called the latent heat of fusion or the enthalpy of fusion, and the temperature at which it occurs is called the melting point.

When you withdraw thermal energy from a liquid or solid, the temperature falls. When you add heat energy, the tem-

perature rises. However, at the transition point between solid and liquid (the melting point), extra energy is required (the heat of fusion). To go from liquid to solid, the molecules of a substance must become more ordered. For them to maintain the order of a solid, extra heat must be withdrawn. In the other direction, to create the disorder from the solid crystal to liquid, extra heat must be added.

The heat of fusion can be observed if you measure the temperature of water as it freezes. If you plunge a closed container of room temperature water into a very cold environment (say  $-20^{\circ}\text{C}$ ), you will see the temperature fall steadily until it drops just below the freezing point ( $0^{\circ}\text{C}$ ). The temperature then rebounds and holds steady while the water crystallizes. Once completely frozen, the temperature will fall steadily again.

The temperature stops falling at (or just below) the freezing point due to the heat of fusion. The energy of the heat of fusion must be withdrawn (the liquid must turn to solid) before the temperature can continue to fall.

The units of heat of fusion are usually expressed as joules per mole (the SI units).

## About the Author



**Sanford Cook** is a consulting and product development resource to the biopharmaceutical packaging industries and is President of Thermal Packaging Solutions, LLC. He has been the chief executive officer, chief engineer and chief marketing executive for global, public, and private companies engaged in the design, documentation, validation, testing, and manufacturing of economical, packaging,

devices, refrigerants, monitors, and operations processes that protect sensitive products against weather and handling vulnerabilities, as well as anti-diversion systems during shipping and storage for more than 25 years. An engineer and a graduate of Business Management, Rutgers University, he holds many patents in the fields of thermal dynamics and devices mentioned above. He has written and published many articles and papers, given numerous speeches, been featured in various national and local media events including the Discovery Channel's Medical Series, Bloomberg Television, ABC News, News Channel 12, the cover page of the Health Section of the Newark Sunday Star Ledger, the Wall Street Journal, and led many seminars to industry and government groups interested in these subjects, primarily in the biopharmaceutical, appliance, and medical device segments. Cook is serving as an officer in the IOPP, Consultants Council.

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