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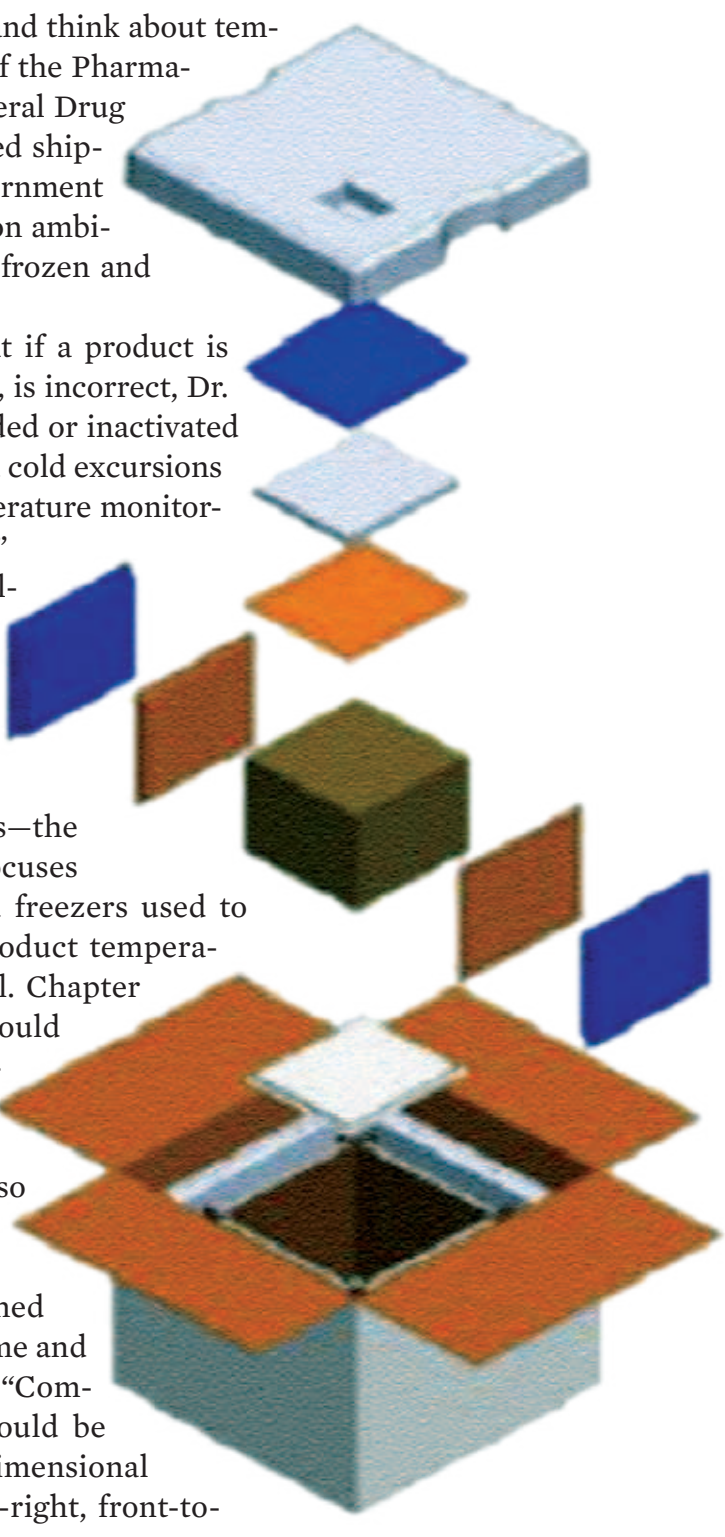
Don't call it 'cold chain'

Avoiding Pitfalls in Temperature Monitoring

LAS VEGAS—You probably think of the process of keeping specialty drugs within a desired temperature range, from the point they leave the manufacturer to the moment the patient opens the package, as "cold chain." But as several experts on the temperature-sensitive distribution process pointed out in a session at the 2017 Asembia Specialty Pharmacy Summit, this misleading moniker detracts from the full scope of what's required to keep these drugs within their ranges.



"I want you to [stop] thinking just about cold chain and think about temperature control," said Rafik Bishara, PhD, the chair of the Pharmaceutical Cold Chain Interest Group within the Parenteral Drug Association. "Cold chain means frozen and refrigerated shipments, but US Pharmacopeia (USP), accreditors, government regulators and manufacturers also want you to focus on ambient and control room temperature, in addition to the frozen and refrigerated conditions."

The typical attitude that "colder is better," and that if a product is cold to the touch when it arrives, that means it's good, is incorrect, Dr. Bishara stressed. "Some drugs and vaccines are degraded or inactivated when frozen. Cold to the touch does not reveal hot and cold excursions during storage and shipping. Hence, concurrent temperature monitoring of the stored and/or shipped product is important."

Dr. Bishara, the former director of quality knowledge management and technical support for Eli Lilly, noted that the shipping packages themselves protect drugs during distribution, but added that temperature monitoring is important to ensure that there was no excursion. USP's Chapter <1079>, Good Storage and Distribution Practices for Drug Products—the latest version of which was released in 2016—also focuses on storage management systems. "Refrigerators and freezers used to store drug products are required to maintain the product temperature between the limits defined on the product label. Chapter <1079> also notes that refrigerators and freezers should utilize recording systems to log and track temperatures, and that alarm systems should be an integral part of such monitoring systems."

Besides refrigerators and freezers, USP <1079> also calls for temperature mapping in pharmaceutical storage areas, shipping facilities, refrigerators and freezers. "A temperature mapping study should be designed to assess temperature uniformity and stability over time and across a three-dimensional space," the section reads. "Completing a three-dimensional temperature profile should be achieved by measuring points at not less than three dimensional planes in each direction/axis—top-to-bottom, left-to-right, front-to-back, where product will be present."

"You will be inspected, by today's current best standards, according to <1079>," Dr. Bishara said, challenging the audience. "Have you mapped your facilities? Where are the hottest and coldest spots? Where are your temperature probes?"

Shipping Studies

According to Mark Maurice, a sales engineer for the supply chain monitoring firm Sensitech, with headquarters in Beverly, Mass., it's important to conduct shipping studies to determine vulnerable points in the temperature-monitoring continuum. The studies should show whether systems meet current extensive accreditation and regulatory requirements. Specifically, such testing should:

- sample internal and external temperatures;
- conduct summer and winter studies;
- create ambient temperature profiles from exterior data for packout design;
- assess how internal temperature is affected by frozen gel packs and interior temperature; and
- assess the correct level of distribution service: courier, overnight priority, overnight same day or ground

To demonstrate some of the most common pitfalls in temperature monitoring, Mr. Maurice presented several sample results of shipping studies. "We analyze thousands of shipments per year; this past year, we did at least 30 studies with pharmacies. We find that often the problem is not the packaging itself—it's the procedures, how you use the packaging. Procedures are involved in 80% of all failed shipments. It's like a puzzle; you can't just throw the pieces into the box. You have to know how they're used."

Table. Effect of Package Design on Temperature Compliance

	Duration in Specified Temperature Range (hours)[a,b]			
Design configuration	**Top Edge**	**Corner Edge**	**Center**	**Middle Edge**
4-sided[c]	54	48	42	48
2-sided	35	7	29	4
2-sided (all frozen)	0	0	53	7

[a] For shipments requiring extended duration or uniform temperature protection within the entire payload space, a 4-sided design offers the greatest degree of protection.

[b] Temperature results outside of 2°C-8°C constituted a failure and were displayed as "0" hours.

[c] 4-sided package designs add more coolant to the payload, extending the duration of time in specified temperature range.

Source: Marianne Hoonakker-Kelly.

Among the sample findings that Mr. Maurice presented was one involving thermal shock. "A majority of you are freezing your products," he said. He described a situation in which frozen gel packs are placed in an expanded Polystyrene (EPS) type of box, with the product placed on top. "Most of the time, the interior product temperature requirements are mandated at the 2° to 8° Celsius temperature range, but immediately after placement in the box, the product's temperature dips down below –5° Celsius, and it spends several hours at that temperature."

Another common pitfall involves placing the package in the refrigerator while awaiting shipping—resulting in more thermal shock. "The frozen gel pack is already doing the refrigeration; you're accelerating that process," Mr. Maurice said. "Many pharmacies we work with are also surprised to see that they're putting their products too close to the frozen gel pack, or that they are using insufficient insulation."

Thermal Shock Protection

To protect against thermal shock, buffer material can be added to prevent the product from getting too cold, said Marianne Hoonakker-Kelly, global market manager at Sonoco ThermoSafe. "Added buffer material can keep the product above 2° C, but there's a tradeoff: buffering can decrease the duration of your temperature protection. Instead of two days, you wind up with something closer to one day. That's not ideal if you have a product that's shipped overnight but may sit on the porch for awhile."

To extend the duration of temperature protection while avoiding thermal shock, Ms. Hoonakker-Kelly described a four-sided box package where more coolant is added around the product space, which can extend the duration of temperature protection. "Four-sided design offers the greatest degree of protection for the longest durations," she said.

Where you measure product temperature does matter as well, she added, showing results of a temperature study that involved three different solutions: a four-sided packout design, a two-sided packout design including buffer material, and a two-sided design with all frozen gel packs without any buffer material. "If I have my product surrounded by two frozen gel packs without any buffer material and measure temperature only in the center of the product space, I may be satisfied with the results that suggest 2° to 8° temperature coverage for 53 hours," she said. "But if I'm more thorough and test the top corner and side edges of the product space in addition to the center, I may find that the solution is completely failing, because the top and corner edges are showing temperatures below 2° Celsius, suggesting thermal shock. I may not consider this design acceptable, because it is not holding the product within the desired 2° to 8° temperature range. For shipments requiring extended duration or uniform temperature protection within the entire product space, four-sided designs offer the greatest degree of protection, while two-sided designs with buffer material can maintain 2° to 8° coverage while avoiding thermal shock."

Audience members brought up the issue of cost when investing in such comprehensive protection. "We use Sensitech now to validate our temperature control, and that almost doubles the cost of our dispensing process," observed one attendee. "Has there been any discussion about the possibility of manufacturers who want this data, and who want their medications delivered in a controlled temperature range, to help reimburse pharmacies for some of these processes?"

Ms. Hoonaker-Kelly suggested that the cost of improved packaging and temperature monitoring be tracked alongside the cost of drugs lost due to improper protection, as well as the "soft" costs of managing phone calls from patients calling in to ask what to do about a drug that feels warm or shows evidence of freezing. "Many of our clients have found that they are realizing cost savings by investing in proper packaging as they are minimizing the hard and soft costs associated with product loss due to improper temperature protection," she said.

—Gina Shaw

The sources reported no relevant financial relationships.